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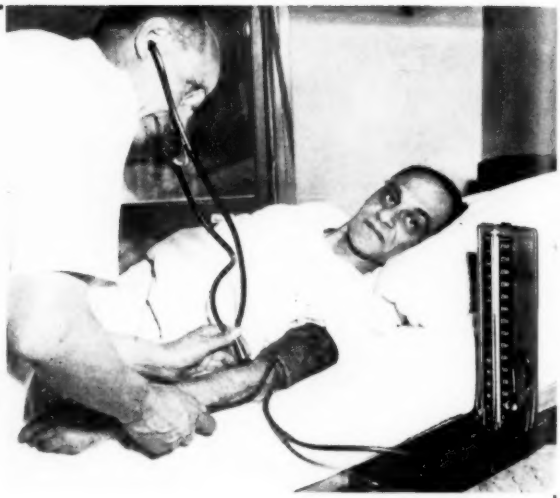

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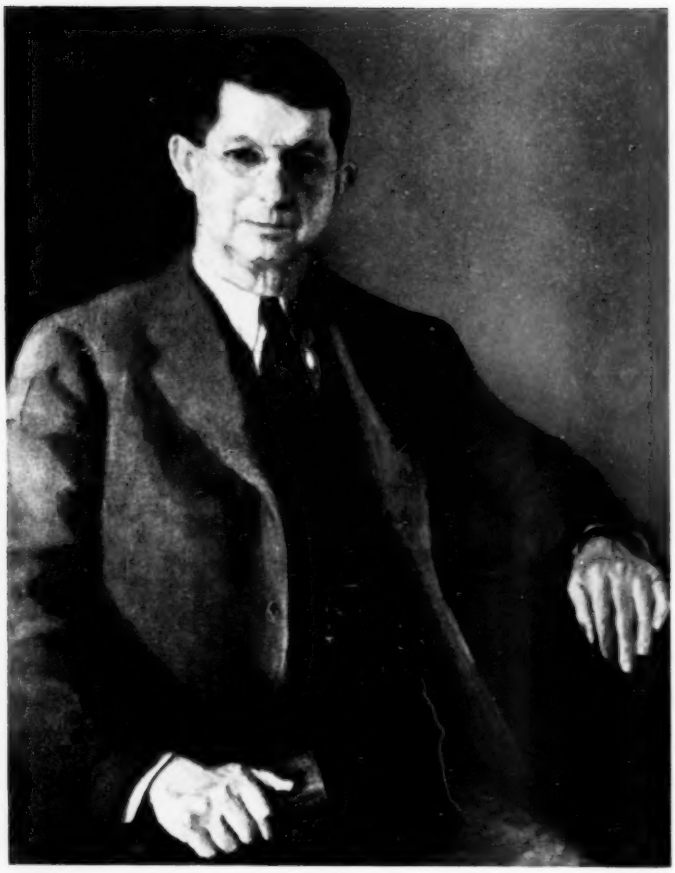

Francis Randolph Packard (1870–1950)
Editor of The American Journal of the Medical Sciences, 1901–1906

OBITUARY

Dr. Francis R. Packard, formerly Editor of this Journal, died at the Pennsylvania Hospital, to which he had given so much of his professional life, on April 18, from complications following a fall in his home a few weeks earlier. Dr. Packard retained his remarkable intellectual qualities unimpaired into his 81st year. Eminent and highly honored in his professional specialty, he was more enamored of the cultural, literary and historical aspects of medicine. He wrote and spoke on such matters extensively and charmingly, his phenomenal memory serving him especially well in extemporaneous remarks. In addition to his participation in the Library Company, the Corporation of the Union Library Catalogue, the Shakespeare Society, the Franklin Inn, the Historical Society of Pennsylvania, and the American Philosophical Society, he was especially devoted to the Pennsylvania Hospital and the College of Physicians of Philadelphia. At the College, as with Osler, his special interest was in the Library, which he served as a Committee member and as Honorary Librarian; when money was needed in a hurry to secure an unexpected rarity, he was not appealed to in vain. As president, he conducted the affairs of the College wisely, and as a life Councillor he attended meetings with great regularity up to the time of his last illness. At the Pennsylvania Hospital he was one of the three internes whom the Hospital required in 1894–5. His connection with the hospital continued throughout his life, in various staff positions and eventually as Keeper of the Archives. Here, too, he was deeply interested in the library, which for nearly a century had been the largest and best in the city. In World War I he served for two years in France with the Pennsylvania Hospital unit (Base Hospital 10, 16 Genl. BEF) and, according to the British procedure, went with a surgical team to a Casualty Clearing Station in times of stress.

Dr. Packard was the son of Dr. John H. Packard, himself an eminent surgeon on the staff of the Pennsylvania Hospital and one-time Vice-president of the College of Physicians. His brother, Dr. Frederick Packard, was one of the most promising of the new type of internists, who unfortunately died of typhoid fever at the age of forty. Francis, the younger brother, was graduated from the biology department of the University of Pennsylvania in 1889 and received his M.D. in 1892. As a widely known oto-laryngologist, he was elected President of the American Otological Society in 1931, and of the American Laryngological Society in 1935, and an honorary member of the Academy of Stomatology.

Dr. Packard's most ambitious historical work was a History of Medicine in the United States (1901, 2d enlarged edition, 1919). He wrote books on Paré, the School of Salerno, the Gold Headed Cane, an abridged History of the Pennsylvania Hospital (1751–1938), a textbook on Diseases of the Ear, Nose and Throat (1909), and also many journal articles. He was the first and only Editor of The Annals of Medical History, which, having survived World War I after twenty-five years as the world's leading journal of medical history, succumbed to the exigencies of World War II.

Dr. Packard succeeded Dr. Alfred Stengel in 1901 as Editor of The American Journal of the Medical Sciences, the sixth in eighty-one years. The short five and a half years of his Editorship (January 1901 to July 1906) were among the most fertile periods of that length in the history of medicine; in them a number of the basic medical sciences made their early important contributions. The theory of mutations, the sex chromosome, Landsteiner's blood groups, opsonins, the complement fixation method, anaphylaxis, the discovery of the inoculability of syphilis into apes, the trypanosome of sleeping sickness, the treponema pallidum, the Wassermann test, Gowland Hopkins' accessory food factors (vitamins), the modern study of internal secretions and the name "hormones" itself, the electrocardiograph — all saw the light in this brief period. The orientation toward biochemistry was accelerated during these years by new societies and the creation of the three chief journals on the subject, and organization of investigative effort was promoted by the foundation of a number of Institutes (Rockefeller, Oswaldo Cruz, Lister, McCormack, Phipps, U. S. Hygienic Laboratory, etc.). Truly a prodigious record! The "Yellow Journal" under Dr. Packard's enthusiastic young editorship kept pace with and not infrequently contributed to these advances and their applications to clinical medicine.

During this period the form of the Journal changed but little from previous years, and in fact has changed but little in the succeeding forty-four years. Original Communications then and now filled most of the space, the remainder being occupied by Book Reviews and Progress Departments. Then and now the Journal had its distinctive yellow cover. The title page had the same wording, though differently typed and spaced. We like to think that this same stability without rigidity is characteristic of the Journal, its owner-publishers, and its editorial boards, and not without its special value in this rapidly changing, restless world.

Dr. Packard liked his editorial job, as he has often assured me, but pressure of other work soon made it necessary for him to resign in favor of A. O. J. Kelly. May his memory long remain green in our publishing and editorial offices!

THE EDITOR

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY 1950

ORIGINAL ARTICLES

ARTERIAL INSUFFICIENCY STUDIED BY SEVERAL PLETHYSMOGRAPHIC TECHNIQUES EMPLOYING OCCLUSION OF THE ARTERIES OF THE EXTREMITY*

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Arterial occlusion of an extremity often aids in determining the most effective type of medical or surgical treatment for patients with peripheral arterial disease by demonstrating the degree of vasodilatation distal to the occluding cuff following release of the arterial occlusion. The present studies were carried out to: 1, compare various plethysmographic techniques for recording the postarterial occlusion changes in blood flow; 2, determine whether or not a 5 minute period of arterial occlusion consistently produced vasodilatation among individuals with functional vascular disease; and 3, describe the characteristics of serial blood flow determinations following 5 minutes of arterial occlusion among normal individuals and patients with various degrees of arterial insufficiency.

Erythema of the skin of an extremity following the release of arterial occlusion has been recognized for many years. Early surgeons noted it after the release of tourniquets following surgery to the extremities and attributed this response to vasomotor paralysis due to pressure on the peripheral nerves. Bier in 1897 demonstrated that reactive hyperemia was independent of this factor in man and in pigs, and in the latter it occurred following the severance of every tissue between the body and the limb except the artery. He and his associates elaborated a system of therapy employing

* Gratitude is expressed to Dr. Burrell O. Raulston for the encouragement and cooperation extended throughout these studies, which were supported in part by a grant from the A. M. Roberts Memorial Fund of the Los Angeles Heart Association.

induced reactive hyperemia for the treatment of many diseases of the extremities of the body[16]. In 1924 Lewis reported reactive hyperemia in denervated human limbs[14]. Lewis and Grant reviewed the literature up to 1925 and studied the physiologic mechanism responsible for this phenomenon by direct observation and plethysmographic flow determinations in the forearm[15]. They concluded that reactive hyperemia was due to the dilatation of the terminal arterioles, arteriolar plexuses, and capillaries. They demonstrated that the dilatation occurred during the period of arterial occlusion and was sustained after release for a period of time roughly correlated with the duration of the occlusion. They felt that the increased blood flow represented a repayment of blood flow debt and was due to a product of metabolism, histamine-like in action, which accumulated in the extravascular spaces during the circulatory arrest and acted directly on the vessels.

Recently a number of investigators have studied the effects of arterial occlusion both clinically and physiologically. Freeman[6] found a correlation, within limits, between the estimated blood flow debt during occlusion and the measured total flow in the post-occlusive state. Rataschow[19] reported consistent differences in the time sequence of color changes after release of arterial occlusion in organic and functional vascular disease. Kunkle *et al.*[10] found that flow, following "maximal" dilatation of the vessels of the foot by heat, was augmented by arterial occlusion and its resultant reactive hyperemia. Eichna and Wilkins[5] found that the greatest flow produced by 5 minutes of arterial occlusion was equal to that of more prolonged occlusion. Abramson, Katzenstein, and Ferris[1], observing normal subjects, found that the greatest augmentation in flow occurred within 90 seconds after release of the occlusion in the hand, forearm and leg. The descent from maximal flow was correlated with the duration of occlusion and the measured reactive hyperemic flow roughly equalled the estimated blood flow debt in the 3 portions of the extremities studied. In half of the subjects with hand flow determinations there was a fall below the control basal flow associated with a "pins and needles" sensation in the fingers. The dip occurred simultaneously in the contralateral hand and the authors postulated that this represented a reflex vasoconstriction due to the painful stimulus of vascular occlusion. Lewis[13] observed the same subjective phenomenon in the fingers after the release of a high occluding cuff, even though a second occluding cuff remained at the wrist. Dauber, Landowne, Katz and Weinberg[4], studying the systemic effects of reactive hyperemia, found an initial drop in systolic and diastolic blood pressure followed closely by a brief increase in cardiac rate in normal subjects. These events did not occur in subjects with thromboangiitis obliterans. They felt that release of arterial occlusion opened low resistance pathways, A-V shunts, and that the elevation of cardiac rate could be attributed to Marey's law rather than to the direct effect of a noxious agent returning to the heart in the blood from the occluded extremity. Landowne and Katz[12] found that flow through the contralateral foot was not materially affected. Short and repeated periods of occlusion following a long period of occlusion produced a peak flow as great as that produced by the initial occlusion. They postulated that 3 factors might influence maximal flow. These were: 1, constricting factors may limit effective dilatation; 2, the vascular bed may reach a maximum state of dilatation which is capable of carrying less blood than the arterial tree can

supply; 3, the resistance offered by vessels not participating in the dilatation may become proportionately greater until the upper limit of flow may be determined primarily by the caliber of the large vessels rather than by the distal arteriolar bed. Landowne[11] developed and demonstrated the latter premise more fully in a study of subjects with thromboangiitis obliterans.

Method. Plethysmographic blood flow determinations were made with a Cambridge pneumo-plethysmograph[2], the laboratory was a soundproof, draught free, pleasantly decorated room with a temperature of 25° C. ± 1°[17]. The subject removed all constrictive clothing and lay quietly in bed covered by a sheet and light blanket. A small plastic cup was sealed to the second toe at the distal flexion crease with a nonconstricting elastic sealing compound. Certain of the subjects were studied with the venous occluding cuff at the digit using a cuff which was constructed of 0.25 inch Penrose drain, cemented to a No. 8F rubber catheter. This was applied with a backing of cellulose tape as close to the plethysmographic cup as possible[3]. The remaining subjects on whom toe flows were determined were fitted with a 12 cm. cloth backed venous occlusion cuff at the ankle[7]. Venous occlusions in the normal subjects was accomplished by quickly inflating the collecting cuff to a pressure of 60 to 75 mm. of Hg. as recommended by Landowne and Katz[12]. In the presence of arterial disease lower pressures were often employed. A standard rib backed pressure cuff 12 cm. in width was used for arterial occlusion and was applied immediately above the knee. The subject was allowed to rest for 20 minutes. A series of 10 control flow determinations were made at 30 second intervals. Following this, arterial occlusion was applied in the manner of Pickering[18]. The leg was elevated to an angle of 45° with the horizontal plane for 30 seconds to facilitate emptying of the venous bed. The occluding cuff was inflated to 70 mm. Hg. above brachial systolic pressure while the leg was still elevated. The leg was then returned to the horizontal position. During the 5 minutes of arterial occlusion the plethysmographic system was closed to test for completeness of arterial occlusion which was indicated by an absence of drift of the recording shadow. The venous occlusion cuff was momentarily inflated to test for artefact. After 5 minutes the occluding cuff was suddenly deflated. Flow determinations were made every 15 seconds for the first 2 minutes, then every 60 seconds for the next 8 minutes. At the end of each experiment the volume of the portion of the toe that had been sealed within the plethysmograph cup was measured by displacement of water. Flow was calculated in the manner of Goetz[8] by determining the angle of rise in the first second after the inflation of the collecting cuff. The volume increase was converted to cu. mm. of flow per 5 cc. of tissue per second. In the results that follow all statements of toe flow are in these terms. Foot flows were determined with a plastic plethysmographic boot with optical recording by means of a modified Frank's capsule as previously described[9]. Flow was calculated in terms of cc. of flow per 100 cc. of tissue per minute.

Subjects for these experiments were 11 normal individuals, 16 patients with arteriosclerosis obliterans, 2 with popliteal artery obstruction, 1 with thromboangiitis obliterans, 2 with vasoneurosis, 1 with coarctation of the aorta, 1 with Lerich syndrome, and 4 with sympathectomies with miscellaneous arterial obliterative diseases (Table 1).

Results. A characteristic normal time flow curve is illustrated in Fig. 1. The portions of the curve were designated the prefastigium, fastigium, postfastigium, and anemocylic interval. The definitions and explanation of these portions are stated in the legend to Fig. 1.

Toe Flow with the Collecting Cuff at the Base of the Toe (Table 1). Three normal individuals, 5 patients with arteriosclerosis, and 1 with thromboangiitis obliterans were studied. Anemocyclia was absent in all determinations. Among normal individuals the prefastigium averaged 40.9 seconds. Among patients with arteriosclerosis obliterans it averaged 50 seconds. The average fastigium among the normals was 41.3 c.mm. per 5 cc. per sec. Among those with arteriosclerosis obliterans and thromboangiitis obliterans the fastigium was considerably less, averaging 26.6 and 33.2, respectively. Among normal individuals the maximum variation in blood flow, as measured from the highest to the lowest flow after the fastigium, averaged 34.8 c.mm. per 5 cc. per sec., as com-

TABLE 1.—CHARACTERISTICS OF SERIAL BLOOD FLOW DETERMINATIONS FOLLOWING ARTERIAL OCCLUSION EMPLOYING VARIOUS PLETHYSMOGRAPHIC TECHNIQUES

Mean, maximum and minimum values for blood flows at certain periods after release of the venous occlusion cuff in normal individuals and in patients with various disease states.

	No. of Subjects	No. of Determinations	Anemocyclia*	PREFASTIGIUM (secs.)			FASTIGIUM (cu. mm./5 cc./sec.)			POSTFASTIGIUM Maximum Variation**			POSTFASTIGIUM Interval between Peak***		
				Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.
Toe Flow with the Collecting Cuff at Base of the Toe:															
Normal	3	11	0	40.9	15.0	60	41.3	24.0	80.0	34.8	8.0	91.0	1.9	1.1	4.0
Arteriosclerosis obliterans	5	9	0	50.0	30.0	120	26.6	1.0	51.0	9.0	5.0	15.2	4.0	2.2	6.0
Thromboangiitis obliterans	1	2	0	75.0	60.0	90	33.2	28.5	38.0			28.2			2.0
Toe Flow with the Collecting Cuff at the Ankle:															
Normal	5	15	0	37.0	15.0	90	21.4	10.5	41.0	8.3	1.0	40.0	2.0	1.2	4.0
Arteriosclerosis obliterans	1	3	3	150.0	120.0	210	4.6	3.5	5.7	1.4	0.5	2.0	6.0	4.0	7.0
Popliteal artery obstruction	2	5	3	187.5	15.0	420	5.1	4.0	7.0	12.2	9.5	14.8	2.25	2.0	2.5
Thromboangiitis obliterans with sympathectomy	1	1	0	120.0			9.0			5.0			3.0		
Coarctation of the aorta	1	1	0	30.0			9.0			5.5			1.1		
Vasoneurosis	2	5	2	88.0	28.0	240	3.8	0.8	13.0	1.8	0.7	3.5	4.4	2.0	8.0
Leriche Syndrome	1	1	0	30.0			7.5			12.3			3.2		
							(cc./100 cc./Min.)								
Foot Flow with the Collecting Cuff at the Ankle:															
Normal	5	5	0	74.0	60.0	120	21.8	11.5	37.5	12.1	3.2	23.8	2.8	1.7	4.5
Thromboangiitis obliterans with sympathectomy	1	1	0	60.0			12.2			4.0			4.0		
Saddle embolus with sympathectomy	1	1	0	60.0			6.7			3.8			3.0		
Left Femoral arterial ligation with sympathectomy	1	1	0	60.0			13.8			6.6			5.0		
Arteriosclerosis obliterans	10	10	4	159.0	30.0	360	7.2	3.2	11.1	3.2	1.2	5.3	2.9	1.6	4.7

* Number of determinations showing anemocyclia.
** Maximum variation in blood flow measured from highest to lowest flow after the fastigium, cu. mm. 5 cc. sec., or cc. 100 cc. min.
*** Interval between peak blood flows in minutes.

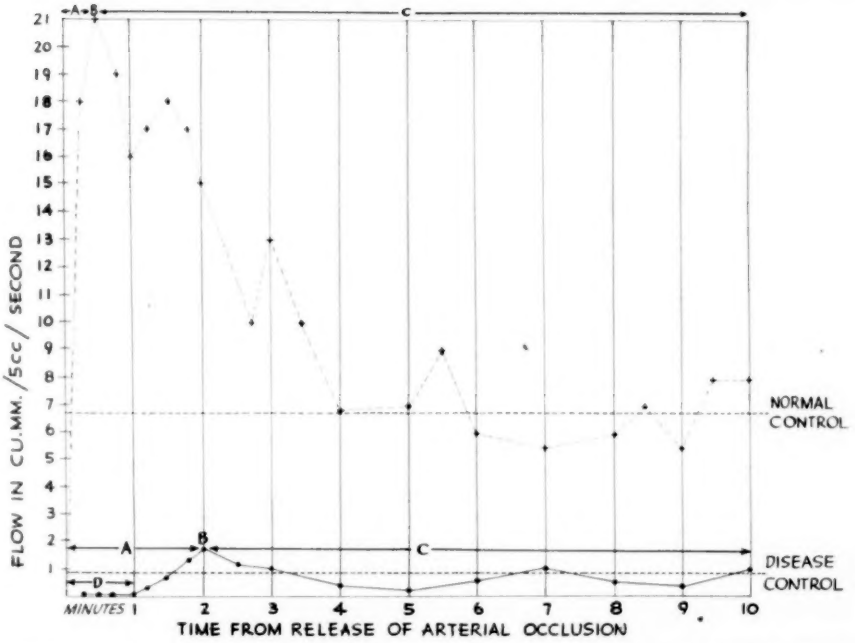

FIG. 1. Typical time flow curves determined by toe plethysmography with the collecting cuff at the ankle. The light dotted line shows a normal curve and its pre-occlusion control level. The solid line is the curve of a patient with arteriosclerosis obliterans and its pre-occlusion control. The portions of the curve are as follows: A) prefastigium, time from release of cuff to maximum flow, B) fastigium, maximum rate of flow, C) postfastigium, time from maximum rate of flow to end of study, D) anemocyclia, time from release of arterial occlusion cuff to first detectable increase in volume.

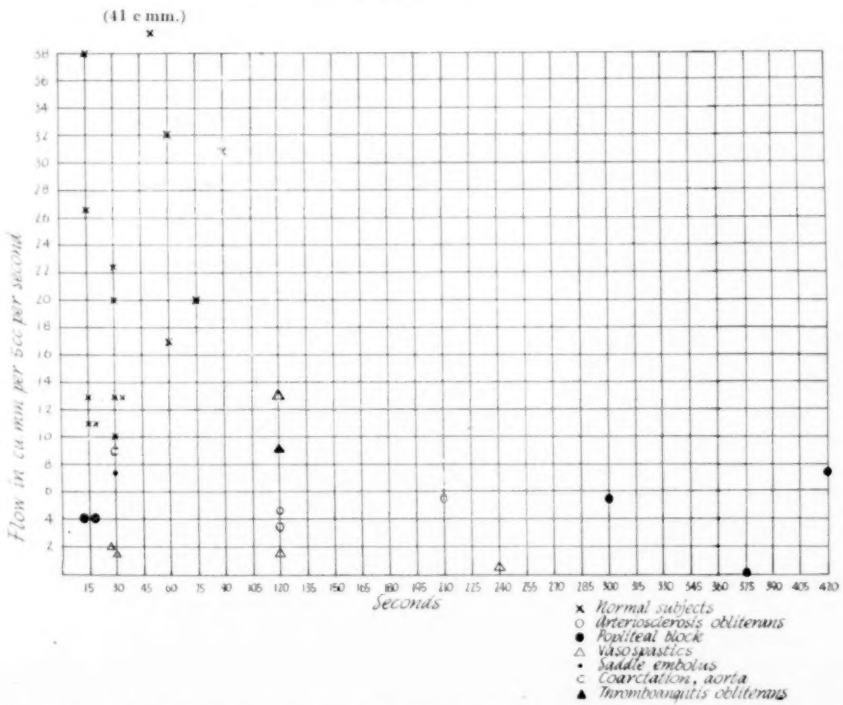

FIG. 2. Height of the fatigium (in c.mm./5 cc. of tissue/sec.) and duration of the prefastigial interval (in seconds) of control subjects and patients with various disease states on whom flow was determined by toe plethysmography with the collecting cuff at the ankle.

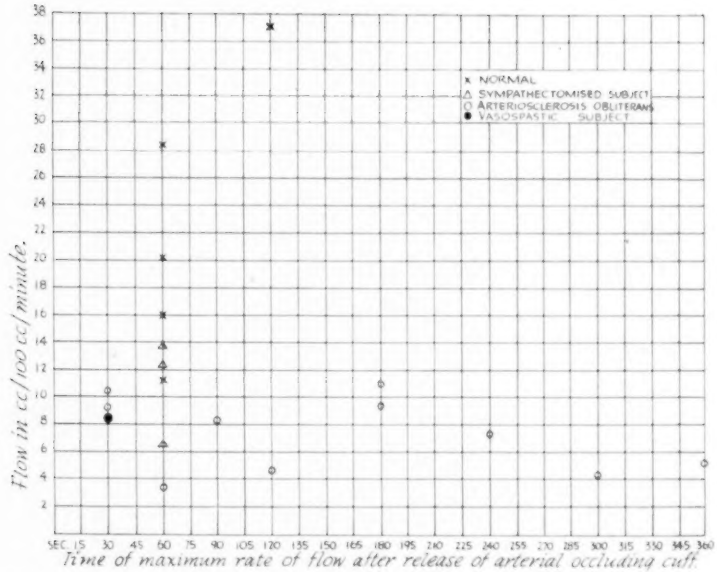
x NORMAL
△ SYMPATHECTOMISED SUBJECT
○ ARTERIOSCLEROSIS OBLITERANS
● VASOSPASTIC SUBJECT
Flow in cc./100 cc./minute.
Time of maximum rate of flow after release of arterial occluding cuff.

FIG. 3. Height of the fastigium (in cc./100 cc. of tissue/minute) and the prefastigial interval (in seconds) of subjects on whom flow was determined by foot plethysmography with the cuff at the ankle.

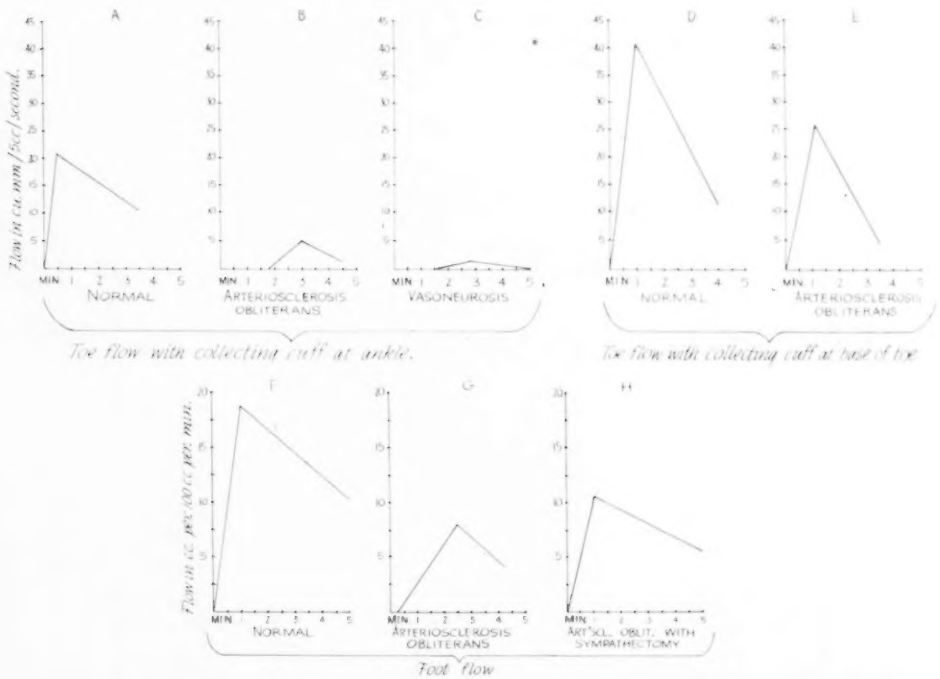

FIG. 4. Average values for blood flows during the prefastigial, fastigial, and lowest average values for flows in the postfastigial periods in normal individuals and patients with various disease states: *a*, 15 determinations on 5 subjects, *b*, 3 determinations on one subject, *c*, 5 determinations on 2 subjects, *d*, 11 determinations on 3 subjects, *e*, 9 determinations on 5 subjects, *f*, 5 determinations on 5 subjects, *g*, 10 determinations on 10 subjects, *h*, 3 determinations on 3 subjects.

pared with 9 among patients with arteriosclerosis obliterans. The interval between peak blood flows in the postfastigium was short among normal individuals (1.9 min.) and longer among patients with arteriosclerosis obliterans (4.0).

Toe Flow with the Collecting Cuff at the Ankle (Table 1). Five normal and 8 abnormal subjects were studied. Anemocyclia was not encountered among normal individuals but was commonly encountered among patients with organic or vasospastic disease. Among normal patients the mean prefastigium was 37 seconds, while in certain patients with arterial occlusive disease it was 187.5 seconds. On 2 patients with vasoneurosis it averaged 88 seconds. Among normal individuals the fastigium averaged 21.4 c.mm. per 5 cc. per sec. Among patients with vasospastic or organic occlusive disease it was less than 10.0. One patient with vasoneurosis had a value of 0.8. Among normal individuals the maximum variation of blood flow in the postfastigial period averaged 8.3 c.mm. per 5 cc. per sec. Five of the 8 patients with vascular disease had variations less than this. The interval between peak blood flows was again short, normal individuals averaging 2.0 minutes. Seven of the 8 patients with vascular disease had intervals greater than this.

Foot Flow with the Collecting Cuff at the Ankle (Table 1). Five normal and 13 abnormal subjects were studied. Anemocyclia was not encountered among normal individuals nor among patients following a lumbar sympathectomy, but was encountered in 4 of 10 patients with arteriosclerosis obliterans. The prefastigia among normal individuals, patients following a lumbar sympathectomy, and patients with arteriosclerosis obliterans averaged 74, 60 and 159 seconds, respectively. The fastigium in the former averaged 21.8 cc. per 100 cc. per min., while in patients with arteriosclerosis obliterans it averaged 7.2. Among normal individuals the maximum variation of blood flow in the postfastigial period averaged 12.1 cc. per 100 cc. per min. Among patients with a lumbar sympathectomy the variations were small, averaging 4.8, while among patients with arteriosclerosis obliterans the average was 3.2. The interval between peak blood flows in the postfastigial period among normal individuals was 2.8 minutes, the interval being greater among patients with a sympathectomy and arteriosclerosis obliterans.

Discussion. For purposes of analysis, the time flow curve following arterial occlusion was separated into several component parts. The maximum rate of flow was termed the fastigium. The period from the release of arterial occlusion to the fastigium was termed the prefastigium. The period from the fastigium to the end of observation, which in our series was 8 minutes, was designated the postfastigium. In some of the subjects with arterial obliterative disease there was a period during which there was no demonstrable blood flow following the release of arterial occlusion. This was termed anemocyclia, denoting the absence of demonstrable circulating blood in the portion of the extremity being examined.

The anemocyclic interval was not encountered in any of our subjects with normal arterial trees. A significant proportion of subjects with arteriosclerosis obliterans, embolic obstruction of the popliteal artery, and one patient with severe vasoneurosis showed anemocyclia of variable duration. Anemocyclia was recorded in comparable cases from toe flow and foot flow with the collecting cuff at the ankle, but not from toe flow with the collecting cuff at the base of the toe. The significance of anemocyclia may rest in local spasm of the artery at the site of arterial occlusion as postulated by Landowne[11]. Another explanation is that

low resistance shunts may be opened proximal to the collecting cuff which keeps the pressure within the distal arterial tree reduced to the point where recordable flow does not occur. It is also possible that the anemocyclic interval represents the time required for blood to fill the arterial tree distal to the occluding cuff to a sufficient degree to produce a detectable increase in the volume of the digit or foot.

The prefastigial period is thought to represent the period of time during which the humoral agent of reactive hyperemia held a predominant role over the vasoconstrictive effect of sympathetic vascular activity. In cases of organic arterial disease the prefastigium was prolonged when measured by toe flow with the collecting cuff at the ankle or toe and with foot flow. The mechanism of this is probably the same as that responsible for anemocyclia. In normal individuals the prefastigium was fairly uniform at about 60 seconds. Several normal subjects with short prefastigia had low fastigia which reflected a high degree of vascular tone. Sympatholytic procedures preceding arterial occlusion often allowed more normal curves to be produced. The prefastigium was in some degree influenced by the experimental conditions. In one case an individual with a previously normal curve responded to a pinch administered 15 seconds after release of arterial occlusion by an immediate decrease in rate of flow which was prolonged and followed in 4 minutes by a slight increase in flow. In another determination on the same subject a deep inspiration during the prefastigial period produced a marked temporary decrease in flow to the digit.

The fastigium was low in patients with organic disease and in those with vasospasm. Five minutes of arterial occlusion at room temperature did not produce the maximum flow that the extremity was capable of attaining. The fastigium represented at least the net effect of: 1, the magnitude of the volume flow rate within the vascular system: 2, the distensibility of the portion of extremity enclosed within the plethysmographic cup; 3, the degree of vasodilatation which occurred during vascular occlusion; and 4, the influence of vasoconstrictive forces such as the degree of sympathetic vascular tone. Among the normal individuals the major factors responsible for variations in the height of the fastigia were the degree of vascular dilatation which occurred during arterial occlusion and the height of sympathetic vascular tone. This was emphasized by the vasospastic individual who showed low fastigia with anemocyclia. Vascular tone remained high in spite of the influence of reactive hyperemia. The fastigia of the subjects with occlusive arterial disease were often limited by a decrease in the magnitude of the volume rate of blood flow which was secondary to arterial stenosis.

The postfastigial period was characterized by a return of flow toward the control flow and by fluctuations in the rate of flow. There was a wide variation in both size and rate of fluctuation within the various groups studied. The mean values showed a tendency toward large fluctuations in normal subjects and low amplitude of fluctuations in vasospastic individuals and patients with arterial obliterative disease. The mechanism of the low amplitude of fluctuations during the postfastigium among vasospastic individuals was probably a relatively fixed high grade vasomotor tone. In patients with organic obliterative arterial disease vasomotor tone probably exerted little control over the rate of flow. Patients with lumbar sympathectomies showed low amplitude of fluctuations which occurred at a slow rate.

Summary. 1. The results of certain

plethysmographic techniques employing arterial occlusion of the extremity were compared among normal subjects and patients with arteriosclerosis, thromboangiitis obliterans, vasoneurosis and other disease states after 5 minutes arterial occlusion. The use of a toe cup with collecting cuff at the ankle proved highly satisfactory as tracings made in this way frequently showed the presence of anemocyclia while this was not detected in tracings recorded with the collecting cuff at the base of the toe. The boot technique was satisfactory in studying the rate of flow to the foot when the major arteries to the foot were stenosed, but was not sufficiently sensitive to demonstrate arterial insufficiency when only small arteries to a portion of the foot were involved.

2. A 5 minute period of arterial occlusion did not consistently differentiate organic arterial disease from vasospastic states. A maximum rate of blood flow following occlusion falling into the normal range did give evidence, however, of a vasospastic element which suggested that good therapeutic results would follow medical or surgical treatment.

3. Time flow curves were plotted and analyzed. The significance of the portions of the curve, designated the prefastigium, fastigium, postfastigium, and anemocyclic interval, was discussed. Normal individuals showed a prompt rise in rate of flow following release of arterial occlusion with all methods of recording. Arterial obliterative disease showed a long prefastigium and low fastigium. A period of anemocyclia was demonstrated in a significant proportion of patients with severe arterial obliterative disease. Vasospastic subjects had a prolonged prefastigium and a low fastigium. The duration of the prefastigium and height of the fastigium in subjects with normal arterial trees were governed to a great extent by the degree of sympathetic tone. In patients with arterial obliterative disease the type of vascular response following arterial occlusion was often controlled by the caliber of the partially obliterated major vessels. Anemocyclia occurred in patients with organic arterial disease and in subjects with vasoneurosis. In the latter sympatholytic procedures often shortened or caused the disappearance of the anemocyclic interval.

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THE TREATMENT OF PERIPHERAL NEUROPATHY IN DIABETES MELLITUS

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Previous studies on vibratory sense in diabetics have revealed an impairment in the transmission of this impulse in such a large number of cases as to indicate that it is almost an integral part of the disease[3]. We have observed that over 93% of all diabetics, whether or not they have neuropathic symptoms, have an impairment in transmission of vibratory sense through

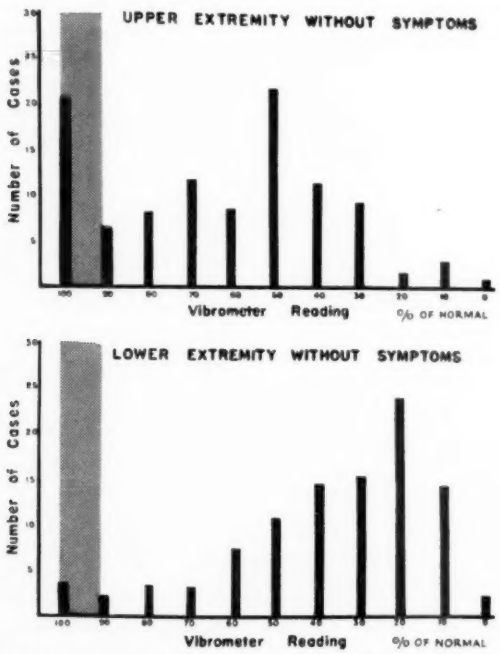

Fig. 1. Chart showing impaired vibratory sense in 100 diabetics *without symptoms* of neuritis. Shaded area shows the range of the normal threshold of response for all ages. Note that there is more severe involvement of the lower extremities than the upper.

the terminal parts of their extremities (Figs. 1 and 2). This was established in a study made with an electrically driven tuning fork with which the amplitude of vibration could be varied, thus making it possible to quantitate the intensity of impairment in vibration sense.

Vibratory sense studies have served as a satisfactory yardstick for estimating the intensity of the existent vibration sense in diabetes mellitus and with an evaluation of the use of vitamin B complex and some of its fractions as supplements in the treatment of diabetic neuropathy.

It is the recognition of the experimental production of polyneuritis in animals by the deprivation of certain fractions of vitamin B complex that has served as a basis for the therapy of the metabolic neuropathy that occurs

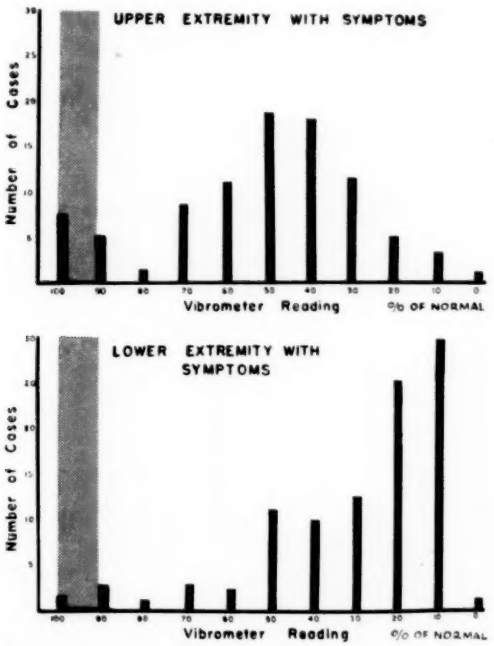

FIG. 2. Chart showing impaired vibratory sense in 100 diabetics *with symptoms* of neuritis. Note here, too, that there is more severe involvement of the lower extremities than the upper.

peripheral neuropathy. What is equally important is that it is possible to use quantitative determination of impaired vibratory sense as a guide to therapy. Thus, reversibility can be recognized by a return of the normal capacity of the peripheral nerve to transmit vibration sense. We have seen this parallel symptomatic improvement with striking regularity.

This paper is concerned with a report of quantitative studies in impaired in diabetes mellitus. It should be recalled that besides thiamine deprivation for producing beri-beri, a severe form of neuropathy has been produced in pigs by feeding a diet deficient in pyridoxine and pantothenic acid[7].

The treatment of diabetic neuropathy consisted in the administration of large doses of vitamin B complex and supplements of several fractions including thiamine chloride and niacinamide.

Although in the past it has not been possible to standardize the dose of vitamin B complex or its fractions, it soon became evident that the more severe the neuropathy, the larger was the dose necessary. The amount of vitamin B complex and its fractions that were administered was far greater than had been previously reported. Although there exists considerable variation in the potency of B complex made by various manufacturers, we selected those which contained, in addition to synthetic supplements, the largest quantity of crude material, especially liver and yeast.

In our opinion, crude liver probably contains hitherto undetermined fractions which may play a role in the therapy of neuropathy. Thus the dose of these agents which we have employed, has, in the more severe cases, consisted of the daily administration of as much as 6 capsules of vitamin B complex or 30 cc. of elixir B complex per day, with the addition of 300 mg. of thiamine chloride and 300 mg. of niacinamide. In order to obtain a good therapeutic effect in the most severe cases of neuropathy, we have found it necessary to administer, in addition, large doses of crude liver extract, B complex and thiamine chloride parenterally. The results are presented in Figs. 3 and 4.

Fig. 3 is a summary of 68 diabetics

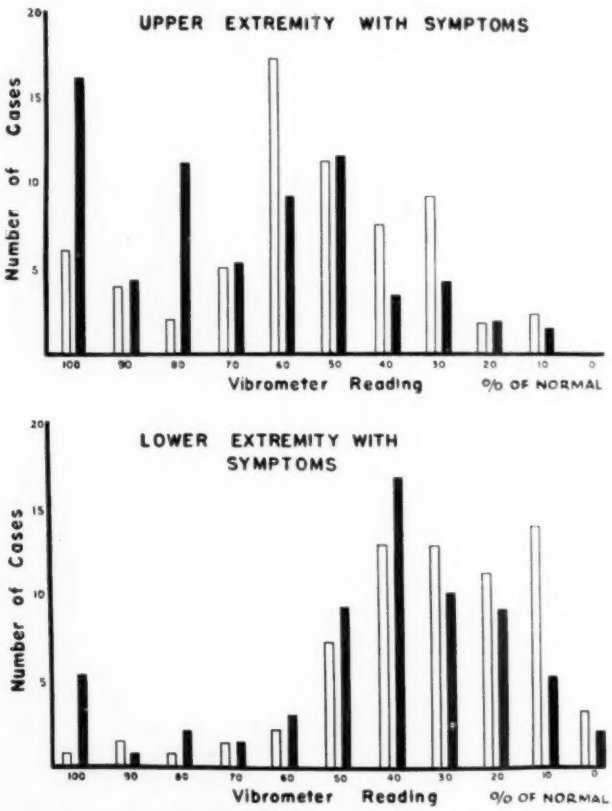

FIG. 3. Results of treatment of 68 diabetics with symptoms of peripheral neuropathy. The open blocks indicate the patients before treatment. The solid blocks show a shift toward the normal following treatment.

with symptoms of peripheral neuritis in whom quantitative studies of vibration sense were made before and after the institution of treatment with vitamin B fractions. The symptoms included numbness, tingling, sensations of pins and needles, burning pain and formication. In the more severe cases where muscle atrophy was seen, weakness of the involved part also occurred. This was not common. It is interesting to note that the symptoms were present in the feet in the majority of cases. It was observed that the magnitude of reduction in readings for vibration sense was greater in the lower extremities than in the upper. Analysis of the cases in Fig. 3 reveals that 60% showed improvement in vibration sense and in some cases even a return to normal. Whereas these vibrometer studies served as an objective test to indicate reversibility in impaired vibration sense in as many as 60% of the cases, actual subjective relief was obtained in 72% of the cases studied.

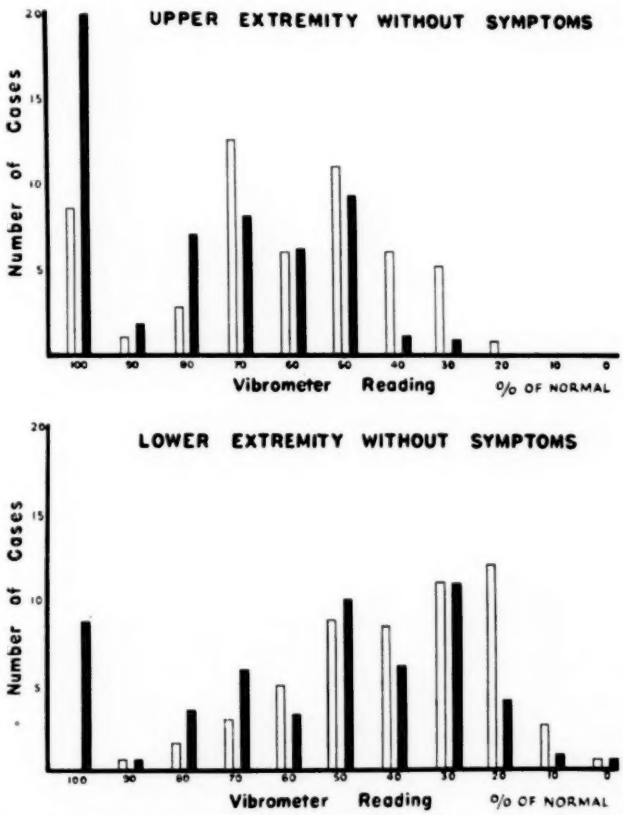

FIG. 4. Results of treatment in 55 diabetics *without symptoms* of neuropathy. Solid blocks show shift toward normal range after treatment.

Fig. 4 is based upon a study of 51 diabetics in whom there was reduced vibration sense *without symptoms* of peripheral neuropathy. Analysis showed improvement in readings after the institution of treatment in 70%; some of them recovered sufficiently to give normal readings.

It can be seen that there occurred a specific shift to the left in the charts indicating that a large number of patients entered categories of either normal or closer to normal thresholds of response to vibration sense stimulation. In those milder cases in whom impaired vibration sense existed without symptoms of neuropathy, a recovery of normal vibration sense took place in as little time as one week.

It is interesting to note that in most severe cases, improvement both in symptoms and vibration sense perception was not apparent for a period of 2 months in spite of most intensive treatment. With few exceptions, ultimate improvement did take place. There was a small number of these patients with severe neuropathy in whom we failed to obtain a therapeutic response regardless of the intensity of therapy. These were patients who presented, in addition, evidence of muscle atrophy either of the thenar eminences or the other intrinsic muscles of the hands and feet. It is worthy to note at this point that in the very severe cases in which we despaired of good results, reversibility in symptoms and impaired vibration sense sometimes followed the daily parenteral administration of 2 cc. crude liver extract (2 units per cc.), 200 mg. of thiamine chloride, 2 cc. of some potent injectable vitamin B complex preparation and 50 mg. of pyridoxine.

Recent reports tend to indicate that vitamin B complex and its fractions, besides having a salutary effect on the well-being of the diabetic, also improves the carbohydrate tolerance of the diabetic, sometimes to the point where the patient is able to discontinue the use of insulin[1]. Although this is not relevant to our present paper, we wish to state that we have employed vitamin B complex and its fractions in many of our cases in larger quantities and for longer periods than is recorded in these reports and were unable to observe any effect upon carbohydrate tolerance.

Discussion. It would appear from these observations that peripheral neuropathy is a component part of the diabetic state since it occurs in almost all diabetics regardless of the duration or intensity of the disease. It appears also that the control of the diabetes by insulin and diets providing physiological needs of carbohydrate, protein and fat neither prevents neuropathies nor cures them when present. As a matter of fact, the converse appears frequently to be true, that the satisfactory control of the diabetes by diet and insulin alone is accompanied by a reduction in vibration sense and the appearance of neuritic symptoms. This has come to be known as post-insulin neuritis[5].

Fig. 5 reveals the result of a study of 9 diabetics in whom vibratory sense was evaluated before and after treatment by diet and insulin without the use of supplementary vitamin therapy. It will be seen that there occurred uniformly a reduction in vibratory sense particularly in the lower extremities. These became evident within 4 weeks after the institution of insulin therapy. Not only is this a common observation but occasionally a patient will complain of classic neuropathic symptoms shortly after the diabetes has come under control with diet and insulin, only to disappear after the institution of the massive B therapy described in this paper.

It would seem that the neuropathies in diabetes represent a disturbance in the metabolism of the anti-neuritic fractions present in vitamin B complex rather than a simple nutritional deficiency of these important components[2,6]. While it is recognized that the physiological requirement of

thiamine chloride is approximately 2 mg. per day[4], it has been our experience that as much as 100 times that amount may be necessary for improvement of the neuropathic state.

Quantitation of the threshold of response to stimulation of vibration sense has served to stress the recognition of the wide incidence of neuropathy in diabetes mellitus and to evaluate therapy. The use of the clinical vibrometer has made it possible to recognize reversibility in impairment in vibratory sense after treatment and to anticipate functional recovery in nerves with improvement in the clinical symptoms of the neuropathies. This instrumental technique has also served to evaluate therapy in the neuropathies and to establish the dose of vitamin B complex and its supplements. Equally important, it has made it possible to see reversibility in impaired vibration sense in sub-clinical neuropathies, to establish the therapy necessary to create recovery of this impaired function and thus establish a basis for the prevention of the development of the neuropathies in diabetes mellitus.

Conclusions. The diagnostic and therapeutic aspects of peripheral neuropathy in diabetes mellitus are discussed.

A quantitative measure of the intensity of neuropathic states and a guide to prophylaxis and treatment are presented.

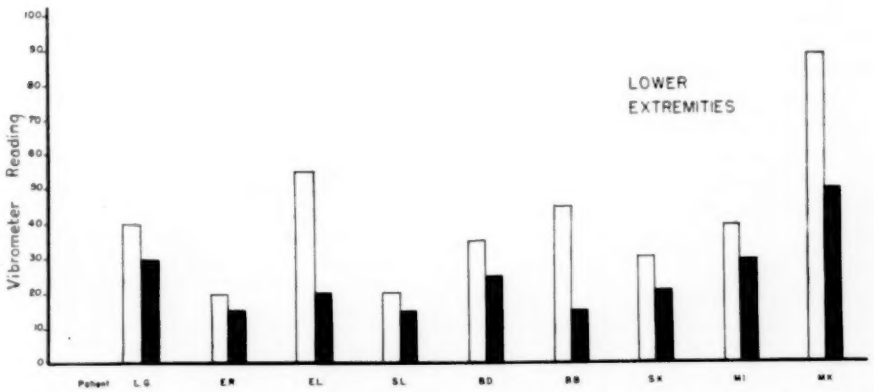

FIG. 5. Further reduction in vibratory sense in lower extremities occurring 1 month following the institution of insulin therapy. Open blocks: before insulin therapy. Solid blocks: readings 1 month after treatment with insulin. No vitamin B was given to these patients.

We are indebted to the Marvin R. Thompson Co. for supplying us with Elixir Vitamin B Complex which was used in this study.

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A STUDY OF RENAL FUNCTION IN PATIENTS WITH MULTIPLE MYELOMA*

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Renal insufficiency is commonly associated with the advanced stages of multiple myeloma, but the nature of the renal lesion has been quite controversial. Pathological changes interpreted as "chronic nephritis" were described in 65% of the reported cases to 1928[11]. Arteriosclerosis and pyelonephritis were noted in many instances by Bell[2], but he regarded them as purely incidental to the disease. Bell stated that the cause of the renal failure was the protein casts found in the renal tubules. Though the casts are assumed to be formed of Bence Jones protein, he felt that the evidence was lacking that the protein injured directly either the glomeruli or tubules. On the other hand, Forbus *et al.*[9] claimed that the Bence Jones protein was toxic to the kidney and described a foreign body reaction of giant cells about the casts within desquamated tubules. In another paper Forbus and co-workers[10] felt that the quantity and duration of the proteinuria were of primary importance in the production of renal lesions, but by animal experiment were unable to reproduce either the casts (without previously induced hydronephrosis) or the foreign body reaction. The pronounced cloudy swelling of the convoluted tubules in these preparations may result from the reabsorption of protein as shown by Oliver[15].

The failure to produce renal injury by the intravenous injection of Bence Jones protein is supported by clinical studies. Bannick and Greene[1] observed several cases of prolonged proteinuria without demonstrable impairment of renal function.

The present study of the renal function in patients with multiple myeloma was stimulated by the observations of Loge and Rundles on the beneficial effects of urethane therapy in this disease[14]. In an effort to establish the pattern of renal functional impairment, and to record any alterations of pattern subsequent to urethane therapy, 18 renal clearance studies have been performed on 15 patients with this disease.

Methods. The diagnosis of multiple myeloma was established by the criteria previously outlined by Loge and Rundles[14]. Only those patients without evidence of other renal disease were selected, and all but 1 had near normal blood pressures and NPN concentrations.

The glomerular filtration rate was determined by the clearance of infused inulin (C_{In}), the effective renal plasma flow by the clearance of p-amino hippurate (C_{PAH}), and the tubular excretory maximum by the excretion of PAH (Tm_{PAH}). The patients were studied in the post-absorptive state. The procedure followed was based on that of Goldring and Chasis[12]. The inulin was determined by the method of Corcoran and Page[6], and the hippurate as described by Smith *et al.*[16]. Each value is an average of 2 or more collection periods of catheter urine, and is corrected to a body surface area of 1.73 sq. meters.

Results. Seven of the patients in this series received treatment with urethane prior to the study of their renal function. It is believed that this therapy did not alter the accuracy of the renal

* This work was supported by a grant from the Life Insurance Medical Research Fund.

TABLE 1.—CLINICAL DATA ON 15 PATIENTS WITH MULTIPLE MYELOMA

	Sex	Age	Probable Duration of Disease	Blood Pressure	Non-Protein Nitrogen mg. per 100 cc.	Serum Alb. Glob. gm. per 100 cc.	Bence Jones Proteinuria	Bone Marrow Plasma cells %	Hematocrit %	Therapy gms. Urethane	Date of Study
E. W. S.	M	42	9 mo.	150/90	36	4.5 2.7	Faint traces	25	48.2	138 (13 Apr. to study)	16 May
W. B.	M	48	?	150/90		4.6 3.0	±	15	38.8	0	3 Mar.
A. P.	M	45	3 yr.	120/60	25	1.9 2.4	++++	24	31.0	0	30 Jul.
				124/80	33	3.9 2.6	++		35.4	243 (2 Aug–17 Sept; 29 Sept–18 Oct.	7 Mar.
J. C.	M	38	1 yr.	110/70	32	4.5 3.4	absent	5	39.7	377 (2 Jul–3 Sept; 6 Feb–)	23 Feb.
S. J. C. (3)†	M	54	8 mo.	130/80	25	4.3 4.4	++++		30.0	268 (3 Feb–10 May)	3 Aug.
C. H. (1)†	F	41	1 yr.	138/86	31	5.0 3.1*	±		41.0	135.5 (21 Feb–9 Mar; 26 Mar–23 Apr)	22 Jul.
M. J. W.	F	52	10 mo.	120/80	42	4.6 2.7	absent	20	40.4	0	15 Oct.
A. R. (2)†	F	48	3 yr.	122/80	40	4.5 2.9*	++	35	38.2	240 (20 Oct–22 Dec)	23 Aug.
				118/70	46	4.4 3.9	±		37.5	120 (23 Aug–25 Sep)	9 Mar.
				115/70	34	3.4 5.7	++		32.8	0 (In relapse)	9 May
P. F.	F	54	8 mo.	120/70	34	3.4 4.7	absent	6	28.6	0	9 Feb.
L. N.	F	46	2–3 mo.	180/100	35	4.0 3.2	absent	7	38.5	12 (14 June to study)	17 June
J. D.	M	58	3–4 mo.	148/90	36	3.3 5.9	±	30	32.8	1.0 (19 May to study)	20 May
J. R.	F	57	10 yr.	142/90	38	4.3 2.0	++	23		0	7 Feb.
C. M.	M	77	6 mo.	120/78	39	4.0 2.5	++	63	33.0	0	3 Jan.
C. K.	M	40	4 mo.	118/84	31	2.0 8.7	+	24	23.8	0	27 Sep.
J. F.	M	72	4–5 yr.	140/70	37	3.2 10.0	++	41	31.7	0	10 Nov.

† (1), (2), and (3) Cases 1, 2, and 3 respectively of Loge and Rundles.[14]
* Serum protein concentrations were grossly abnormal prior to the time of study.

function studies. In tissue culture studies with the chick mesonephros, Chambers, Beck and Belkin[5] found concentrations of ethyl urethane from 4.3 to 6.0% to be necessary to impair phenolsulphonphthalein transfer, and that concentrations of less than 3% were without effect. At therapeutic dosages of 4.0 to 6.0 gm. per day orally, the body fluid concentration in the average patient must have been greatly below that level. In the present series of patients, 4 of the 6 with the least renal impairment had received the drug prior to these studies in amounts up to 377 gm. over a period of months, and 2 were taking urethane at the time of the study.

The data pertaining to the renal function studies on this group of 15 patients with multiple myeloma are shown in Table 2. As observations were made in both male and female patients, each clearance value is also expressed as a percentage of the normal mean as reported by Smith[17]. The patients are listed in order of decreasing percentage of the normal rate of glomerular filtration. Shown in Table 1 are the pertinent clinical, hematological and biochemical data at the time of the renal study.

The glomerular filtration rate, renal plasma flow and hippurate Tm ranged from normal to greatly depressed values. The glomerular filtration rate in this disease is frequently impaired to a greater extent than the ability of the tubules to excrete p-amino-hippurate. This relationship is shown

TABLE 2.—RENAL STUDIES ON 15 PATIENTS WITH MULTIPLE MYELOMA

	Glomerular Filtration Rate		*Renal Plasma Flow*		*Filtration Fraction*	*Tubular maximum PAH*	
	cc./min.	*% nor.*	*cc./min.*	*% nor.*		*mg./min.*	*% nor.*
E. W. S.	141	108	624	89	0.23	70.0	90
W. B.	140	107	632	91	0.22	69.5	90
A. P.	117	89	455	65	0.26	73.9	95
	92	69	663	95	0.14	69.5	90
J. C.	106	81	660	95	0.16	94.3	122
S. J. C. (3)*	106	81	440	63	0.24		
C. H. (1)*	94	80	514	86	0.18	60.0	77
M. J. W.	85	73	460	77	0.19	55.5	72
A. R. (2)*	81	70	358	60	0.23	73.8	95
	53	45	355	60	0.15	55.1	71
	60	51	403	68	0.15	52.6	68
P. F.	78	66	262	44	0.30	63.4	82
L. N.	67	57	319	54	0.21	65.6	85
J. D.	74	56	527	76	0.14	63.7	82
J. R.	40	34	211	36	0.19	35.8	46
C. M.	45	34	312	45	0.14	66.3	86
C. K.	37	28	246	35	0.15	30.5	39
J. F.	34	26	268	38	0.13	34.4	44

* Cases 1, 2, and 3 respectively of Loge and Rundles.[14]

graphically in Figure 1, where the filtration rate is plotted against the tubular excretory maximum, both expressed as a percentage of normal. In all but 4 instances, there is relatively greater impairment of glomerular filtration, and these 4 patients were among those with good kidney function.

The filtration fraction did not show a consistent pattern. In most patients with values for renal plasma flow below 300 cc., the renal plasma flow

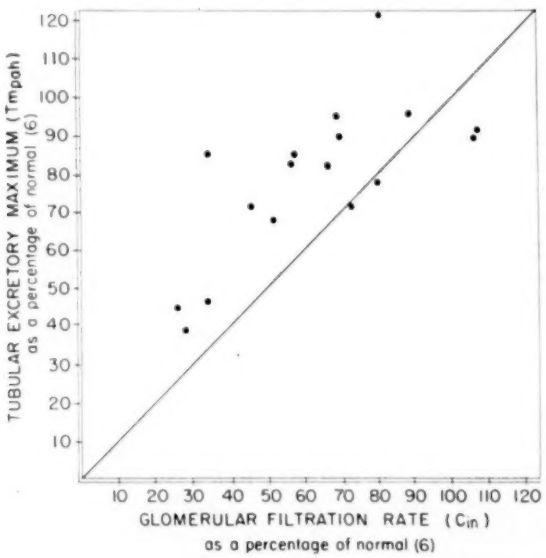

Fig. 1. The comparison of glomerular filtration rate and tubular excretory maximum in patients with multiple myeloma.

as recorded is very likely too high. Kidney disease sufficiently severe to interfere with plasma flow to this degree, usually results in decreased tubular extraction of PAH at low plasma concentrations[4]. In the patients with low renal plasma flow, the filtration fractions as recorded here are probably falsely high.

No simple correlation between the renal studies and other manifestations of myeloma could be found. Proteinuria was absent in 3 patients with considerable renal impairment. In 2 patients (A.P. and S.J.C.) with relatively good renal function the daily excretion of Bence Jones protein was approximately 20 gm.; in 1 of these (A.P.) the proteinuria was known to have existed for over 2 years. Likewise, the concentration of serum globulin was normal in Patient C.M., who had reduced renal function, although abnormal in several patients with considerably better kidney function. There was no correlation between renal function and the number of plasma cells in bone marrow studies, the blood pressure, or the NPN concentration.

Discussion. The occurrence of Bence Jones proteinuria and renal failure in patients with multiple myeloma has led to the simple assumption that the renal failure results from obstruction of the tubules by precipitated protein. The present observations

neither support nor deny this hypothesis. They do raise the following points for future study.

There is no relation between the amount of proteinuria and the degree of renal damage. This is not conclusive evidence against the thesis of damage from simple protein precipitation because Bence Jones protein does not seem to be a single homogeneous substance. As there appear to be several varieties of Bence Jones protein, the renal damage may be found to correlate with the type appearing in the urine, rather than the amount.

The glomerular filtration rate (GFR) was in general depressed more than the hippurate Tm. Patients with glomerular nephritis show similar depression of the GFR/Tm ratio until the diodrast Tm drops below 60% of the normal value. However, the glomerular filtration fraction does not show the consistent lowering which has been shown to be characteristic of glomerular nephritis in the absence of hypertension[8]. While the filtration fraction is low in some of the patients with advanced renal lesions, the finding is not consistent enough to be used as a strong argument for the presence of a primary glomerular lesion. A review of Bell's work[2] shows that he described glomerular lesions in 7 of the 11 cases studied, whereas many casts were found in 5 and tubular atrophy in but 3. He noted an increase of glomerular epithelium, thickening of the basement membrane, a protein deposition in the glomerular capillaries.

In tubular obstruction alone one would expect either proportional depression of glomerular and tubular functions, as from precipitated protein, or the development of the lower nephron syndrome in which tubular damage predominates. Corcoran and Page[7] induced the lower nephron syndrome in dehydrated and acidotic dogs by the intravenous injection of solutions of hemoglobin and myoglobin. The maximal tubular excretion of diodrast was depressed more than the glomerular filtration rate. These changes were in the opposite direction from those reported here in patients with myeloma.

These data demonstrate anew the difficulty in attempting to derive a correct picture of abnormal renal morphology from functional studies. The patients reported in the literature[2,9,13] in whom tubular cast formation was most prominent uniformly have had a terminal clinical history of considerable dehydration and azotemia often associated with severe vomiting or coma. Blackman *et al.*[3] called attention to the role of oliguria, high urinary salt concentration and acidosis in the production of tubular damage. By contrast the group reported here were ambulatory, well hydrated and without azotemia. It is possible that a considerable portion of the cast formation may be a terminal event related to the precipitation of Bence Jones protein because of dehydration and acidosis. The intravenous injection of Bence Jones protein in dogs with dehydration and acidosis would be of interest. Under these conditions tubular casts of Bence Jones protein might be found.

Conclusions. 1. Eighteen renal clearance studies have been performed on 15 patients with multiple myeloma who did not present evidence of other renal disease. The glomerular filtration rate (C_{In}), effective renal plasma flow (C_{PAH}) and maximal tubular excretory capacity (Tm_{PAH}) were determined.

2. There was no simple correlation between the renal functional impairment, the age of the patient, the duration of the disease, the presence or degree of Bence Jones proteinuria, the hematological findings, or the quantity of abnormal serum protein.

3. The glomerular filtration rate was found to be impaired to an equal or greater extent than the tubular excre-

tory capacity. This finding was more evident in patients with poorer kidney function. The filtration fraction was not consistently altered.

4. No final conclusion can be drawn from these studies as to the cause or morphological site of the renal lesion in multiple myeloma. The lowering of the GFR/Tm ratio suggests that glomerular as well as tubular changes occur, but the absence of a consistent fall in filtration fraction does not indicate a primary and predominant glomerular lesion.

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THE USE OF PHENYLACETYLUREA (PHENURONE) IN CONVULSIVE DISORDERS

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From the time of the introduction of phenobarbital by Hauptmann[7] until the present, synthesis and clinical evaluation[8,9] of anticonvulsant drugs has resulted in an ever increasing number of more and more effective compounds for use in the control of epilepsy and related disorders. Although some of these compounds, such as the sulfones, are chemically dissimilar, the majority of them are urea derivatives, such as the hydantoins and barbiturates. Further investigation of the urea derivatives led to investigation of the anticonvulsant properties of the acetyl urea derivatives by Spielman[11] and by Everett and Richards[2]. In the aromatic series, phenylacetylurea (Phenurone) has the greatest anticonvulsant properties and is the subject of this report.

Phenylacetylurea, or Phenurone*, is a straight chain compound and may be considered as an open model of the barbiturate nucleus less 1 carbon atom[11], or as the result of the hydantoin ring[13], or as a barbiturate with 1 corner knocked off[10].

Phenylacetylurea is practically insoluble in water and is odorless and tasteless. Acute and chronic studies in animals[1] indicate that the drug has a low toxicity when given orally. The growth curve of rats receiving a diet containing 1% phenylacetylurea is significantly slowed.

Most investigators have come to believe that no individual test of anticonvulsant action in animals accurately predicts the effectiveness of a drug as an anticonvulsant in human beings. It is probable that a battery of procedures[13], including the maximal electro-shock seizure test, normal electroshock threshold, hydration electroshock threshold, metrazol seizure test and possible other tests give the best overall picture of the anticonvulsant action of the drug. The protective index[12] of phenylacetylurea on the above mentioned tests exceeds that of diphenylhydantoin sodium (Dilantin), phenobarbital (Luminal) and trimethadione (Tridione).

To date the only reports on the clinical use of phenylacetylurea have been those of Gibbs and his associates[5,6]. These investigators administered the drug to patients whose seizures had been resistant to all other forms of therapy in the past. They found that 33% of the patients with grand mal, 46% with petit mal and 50% of those with psychomotor disorders were greatly improved. In 20% of their cases pre-existing personality disorders were exaggerated. This change in personal

* The Phenurone used in this study was supplied through the courtesy of Abbott Research Laboratories, North Chicago, Ill.

ity was more common in patients suffering from psychomotor disorders than in the other types. Their postulation was that the psychiatric disorder in such patients is antithetic to the epilepsy[4]. They also noted a number of additional toxic manifestations such as anorexia, weakness, headache, insomnia, palpitation and dermatitis. These toxic actions made it necessary for them to discontinue the drug in 41% of their cases. Forster[3] has reported 1 case of fatal aplastic anemia occurring during administration of phenylacetylurea.

Method. Phenylacetylurea was administered to 32 patients seen in the Clinic for Convulsive Disorders of this college and in the private practice of 1 of us. All of these patients were subject to recurrent disorders of consciousness. Routine studies included neurologic examination, electroencephalogram, and skull Roentgen-ray examinations. The majority of these patients returned for observation at 2 to 4 week intervals. The patients had been under observation and treatment for periods of from 3 to 36 months (average 15.9 months). The types of seizures from which the patients in the group suffered were as follows:

Grand mal seizures only	3 patients
Grand mal and petit mal	1 patient
Grand mal, petit mal and psychomotor	2 patients
Grand mal and psychomotor	16 patients
Grand mal and myoclonic	1 patient
Psychomotor only	7 patients
Petit mal only	1 patient
Tonic stupor	1 patient

Phenylacetylurea was administered for periods ranging from 2 weeks to 10 months (average 4.2 months). Other anticonvulsant drugs were not discontinued when administration of phenylacetylurea was begun. The patients were closely observed for toxic manifestations. Complete blood counts and urinalyses were performed regularly. In 5 cases (16%) the drug was discontinued after the patient had taken it from 2 weeks to 8 months, due to the development of toxic manifestations. In 5 cases (16%) phenylacetylurea was eventually discontinued as it did not seem to be producing any improvement in the seizures. It was necessary to discard only 1 case because of poor cooperation on the part of the patient.

A statistical analysis of the cases was made and the average monthly frequency of the various types of seizures was established for: 1, "The base line": that is before the patient came under our observation; 2, "Best prior treatment": frequency under the most effective treatment prior to the administration of phenylacetylurea; 3, "On phenylacetylurea": during the administration of phenylacetylurea alone or in combination with other drugs. For various reasons it was not possible to obtain a "base line" frequency in 8 patients. This necessitated use of the condition at the time of the "best prior treatment" in evaluating the effectiveness of phenylacetylurea for the group as a whole.

The degree of improvement after administration of phenylacetylurea was correlated with age, sex, age at onset of the convulsive disorder, etiology, dosage of phenylacetylurea and other factors. The improvement was calculated on the basis of improvement in all types of seizures. Each seizure type was considered as one unit. This explains the fact that although there were only 23 patients in whom a "base line" could be established, there were 37 seizure types involved in determining the average improvement of this group.

Results and Comment. In 23 cases there was an average improvement in the seizures of 62.8% as compared with the "base line" during administration of phenylacetylurea. In 31 patients an average improvement in the seizures of 59.5% occurred during administration of phenylacetylurea as compared with the "best prior treatment".

The average improvement in seizures according to the type seizures experienced (compared with "best prior treatment") was as follows:

Entire group (37 seizure types)	59.5% improvement in number of seizures
Grand mal (21 cases)	53.8% improved
Petit mal (3 cases)	33.3% improved
Psychomotor (24 cases)	66.3% improved
Myoclonic (1 case)*	No improvement
Tonic stupor (1 case)	85.0% improved**

*This patient has massive myoclonic jerks and not the familial myoclonus which has been reported to show improvement on phenylacetylurea by investigators at the Caro State Hospital (Michigan).

**The seizures in this patient were greatly increased in number by all forms of treatment including phenylacetylurea but phenylacetylurea caused the least exaggeration of any drug.

It appears from this analysis that phenylacetylurea is most useful in psychomotor disorders and may produce some benefit in grand mal. Some of the improvement noted in grand mal disorders may be attributed to use of other medications as these were continued and sometimes increased in dosage during administration of phenylacetylurea. This does not seem to account for the improvement in the psychomotor disorders, for in most instances the psychomotor seizures had failed to respond to maximum doses of other medications.

No significant correlation was found between the degree of improvement during administration of phenylacetylurea and the age and sex of the patient, age at onset of the disorder or etiology of the disorder.

The maximum dose of phenylacetylurea administered was 6.0 gm. daily, the minimum 0.5 gm. daily, and the average dose was 2.08 gm. daily. Of the 30 cases, 21 received 0.5 to 2 gm. daily and 9 received 2.5 to 6 gm. daily.

From Table 1 it appears that with an adequate dosage of phenylacetylurea maximum improvement in seizures is reached during the first 2 months and that little improvement can be expected to occur thereafter. Although some patients received as high as 6.0 gm. of phenylacetylurea daily, the average improvement on 2.0

TABLE 1.—RESULTS OF TREATMENT OF 30 CASES.

Months Drug Administered	*Number Cases*	*Number Seizure Types*	*% Improvement*
0– 2	10	16	45
3– 4	6	11	64
5– 6	6	9	68
7– 8	5	9	50
9–10	3	5	66

TABLE 2.—TOXIC EFFECTS ASSOCIATED WITH ADMINISTRATION OF PHENYLACETYLUREA.

Symptoms	*No. Cases*	*% Cases*	*Graded Severity of Individual Cases*	*Remarks*
DERMATITIS	2	6.5	2,2	One patient had dermatitis on other drugs
C. N. S. SYMPTOMS	15	45.1		
Drowiness	8	25.8	3,2,1,1,2,1,3,3	Necessitated discontinuing one drug in 1 case
"Nervousness"	2	6.5	2,2	
Excitement	4	12.9	4,1,1,2	
Personality Change	3	9.7	2,2,4	
Visual Disturbances	4	12.9	4,1,1,2	
Psychosis	1	3.2	4	Schizophrenic reaction
Headache	3	9.7	2,3,2	
Insomnia	3	9.7	3,4,3	
"Dizziness"	1	3.2	1	
GASTROINTESTINAL	8	25.8		
Anorexia	4	12.9	2,3,3,2	
Nausea	2	6.5	2,2	
Vomiting	1	3.2	1	
Indigestion	3	9.7	2,1,3	
Abdominal Pain	4	12.9	4,3,2,2	
Liver Damage	1	3.2	1	Slight increase of icterus index
WEIGHT LOSS	2	6.5	2,3	
WEAKNESS	2	6.5	2,2	

gm. per day or less was 58.5% as compared with 61.8% for doses in excess of 2.0 gm. per day. It was our impression that the curve of improvement flattened considerably in the higher dosage ranges. The seizures generally tended to recur from 1 to 3 days after withdrawal of phenylacetylurea but in 2 patients there were remissions of 10 weeks and 4 months, respectively, after withdrawal of all medication.

The toxic effects attributed to phenylacetylurea are shown in Table 2. It will be noted that the greatest number of toxic symptoms were related to the central nervous system. Toxic symptoms referable to the gastrointestinal system were next in frequency and many of these may have been produced by neural mechanisms.

All of the patients who showed personality changes as a toxic manifestation suffered from psychomotor seizures. Two of the patients showing the greatest change had pronounced preexisting psychoneurotic tendencies. One patient who developed a psychosis had a schizoid personality before phenylacetylurea was administered. Only 1 case showed any evidence of liver damage and this consisted of anorexia, nausea and slightly elevated icterus index. All of these symptoms subsided rapidly on reduction of the dosage from 1.5 to 1.0 gm. daily. In 1 patient insomnia was extreme and she developed a dread of night similar to that seen in delirium tremens. It is interesting to note that the symptoms persisted for 5 days after withdrawal of phenylacetylurea but disappeared rapidly after administration of 100 mg. of thiamine hydrochloride parenterally for 2 days. In view of Gibbs' assertion[6] that the patient with anorexia in his series responded well to administration of vitamin B complex, there appears to be a possibility that phenylacetylurea may exert some antithiamine effect and that this may be responsible for some of the toxic symptoms.

One patient took 6.0 gm. of phenylacetylurea in a single dose in a suicidal attempt. Ataxia and confusion appeared and persisted for 2 days but no other untoward effect was noted.

In this small series of patients, dermatitis appeared with about the same frequency as it has been found in cases treated with methylphenylethyl hydantoin (Mesantoin) and diphenylhydantoin (Dilantin), and more frequently than with trimethadione (Tridione). The hypertrophy of the gums which is found in 25 to 50% of patients receiving diphenylhydantoin was not noted, but gastrointestinal disturbances were seen with about equal frequency. Ataxia, nystagmus, drowsiness, tremor and dysarthria are frequently found when high doses of the hydantoins or phenobarbital are being administered, but these symptoms were seldom seen with phenylacetylurea. The photophobia and bone marrow depression resulting from trimethadione administration was not observed during use of phenylacetylurea.

In a few cases it was not possible to suppress the seizures completely with any tolerable dose of the drug administered during the waking hours, but the seizures were better controlled when the drug was administered on an "around the clock" 4 hour schedule. As the duration of the action of the drug is 4 to 5 hours it appears that suppression of the dysrhythmia continually may produce a greater reduction of seizures than administration of the drug only during the day.

A few illustrative case reports follow.

Case Reports. CASE 1. *Remission of Psychomotor Epilepsy and Disappearance of EEG Abnormality Following Administration of Phenylacetylurea.* R. L., a 15 year old colored male, began having 3 to 4 psychomotor seizures daily 3 years previously. The neurologic examination was entirely normal.

An electroencephalogram showed pronounced paroxysmal abnormalities of the psychomotor variety. He was followed regularly in the Convulsive Clinic for over a year and received maximal doses of trimethadione, methylphenylethyl hydantoin, diphenylhydantoin sodium, amphetamine, desoxyn, glutamic acid, amino acid supplements, mebaral, phenobarbital and bromides. Under these programs of treatment his seizures continued to occur from 1 to 3 times daily. Finally all medication were discontinued due to lack of benefit. Administration of phenylacetylurea was begun in August 1948, with a dosage of 1.5 gm. daily. The following month he had 2 psychomotor seizures but thereafter remained seizure free. On January 4, 1949, phenylacetylurea was withdrawn. Repetition of the electroencephalogram on April 26, 1949, showed a complete disappearence of the profound abnormalities noted in the 2 records obtained prior to administration of phenylacetylurea (Fig. 1). He remained completely free of all seizures until May 17, 1949, when he had 2 psychomotor seizures. Phenylacetylurea was again administered in the same dosage and he has remained seizure free to date. No personality changes were noted during or following administration of phenylacetylurea.

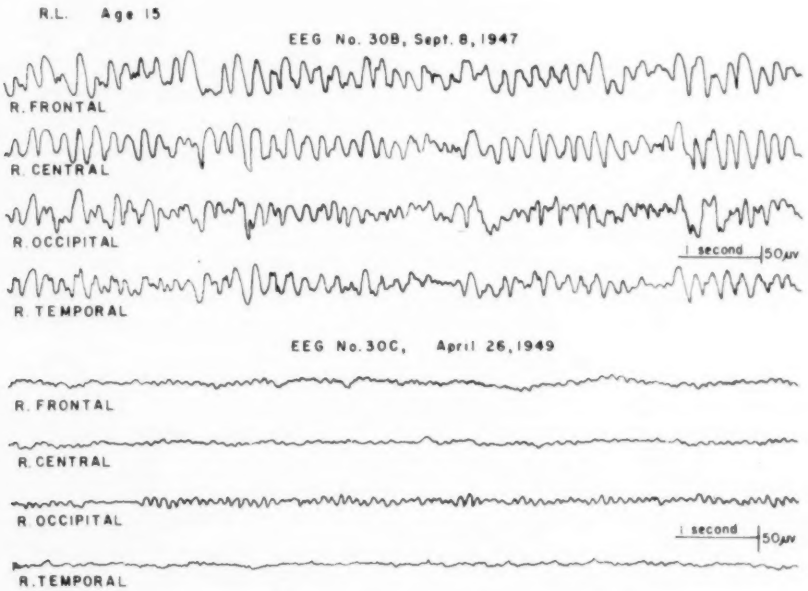

FIG. 1. Effect of Phenylacetylurea on E. E. G.

CASE 2. *Psychosis During Administration of Phenylacetylurea with Remission of Psychomotor Seizures.* J. C., a 25 year old white man who had grand mal and psychomotor seizures since the age of 7. A neurologic examination was normal. An electroencephalogram was abnormal, showing excessive fast and excessive slow activity without any specific "epileptic" patterns. He was a shy, rather introverted individual over-protected by his parents. On treatment with diphenylhydantoin sodium, phenobarbital and methylphenylethyl hydantoin his grand mal seizures showed an improvement of 75% but the psychomotor seizures continued unabated. Administration of phenylacetylurea was begun and gradually increased to 2.5 gm. daily. One month after institution of this treatment he developed increasing irritability, auditory and visual hallucinations, delusions of persecution and incoherent speech. These symptoms continued following the discontinuance of phenylacetylurea and his psychosis necessitated commitment to the state mental hospital for 7 weeks. There he received insulin subshock therapy and the psychosis improved so that he was parolled. Three weeks later he again became psychotic and was re-admitted to the state mental hospital. The patient has had no psychomotor seizures since the first dose of phenylacetylurea. All medications were withdrawn at the time the psychosis first developed and although

grand mal seizures occurred, psychomotor seizures remained in complete abeyance.

CASE 3. *Improvement of Psychomotor Seizures Due to Phenylacetylurea–Toxic Dermatitis.* Mrs. R. E. C., a 23 year old female had had cryptogenic, grand mal and psychomotor seizures since the age of 14 months. The grand mal seizures were completely controlled on a combination of diphenylhydantoin sodium, phenobarbital and methylphenylethyl hydantoin, but she continued to have an average of 300 psychomotor seizures per month. After administration of 1.5 gm. of phenylacetylurea daily the psychomotor seizures were reduced to an average of 30 per month but she developed a widespread morbilliform pruritic dermatitis. After discontinuance of phenylacetylurea the psychomotor seizures recurred in full force. Phenylacetylurea was again started and an antihistaminic preparation was given concurrently. The phenylacetylurea was increased to 4.0 gm. daily without recurrence of the dermatitis and with a further reduction in seizures to an average of 20 monthly. In addition to the numerical reduction of the seizures they became less severe so that only rarely was there complete amnesia for the attack.

Summary and Conclusion. 1. Phenylacetylurea (Phenurone) was administered to 32 patients suffering from a convulsive disorder.

2. The improvement in the number of seizures as compared with the best prior treatment was as follows: Grand Mal, 54%; Petit Mal, 33%; Psychomotor, 66%.

3. Some of the improvement in the grand mal seizures could be attributed to medications other than phenylacetylurea, but phenylacetylurea appears to be responsible for most of the improvement in the psychomotor seizures.

4. The relative maximal improvement occurred within the first 2 months after administration of phenylacetylurea was begun, and with doses of 2.0 gm. per day or less.

5. Toxic symptoms, chiefly referable to the central nervous system or gastrointestinal tract, occurred in many cases, but necessitated discontinuance of the drug in only 16%.

6. Phenylacetylurea appears to cause considerable improvement in psychomotor disorders, slight improvement in grand mal seizures, and little or no improvement in petit mal, tonic and myoclonic type seizures.

Since preparation of this report, the authors have seen 1 additional case of psychosis and 1 case of severe leukopenia (1200 leukocytes) occurring during the use of phenylacetylurea. The psychosis disappeared rapidly after withdrawal of the drug and administration of insulin sub-shock therapy. The leukopenia disappeared after phenylacetylurea was withdrawn and penicillin administered.

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ABNORMAL ELECTROKYMOGRAMS FROM THE WALL OF THE VENTRICLE WITH AND WITHOUT EVIDENCE OF MYOCARDIAL INFARCTION*

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The recent development of methods for recording the motion of the heart's border in man has made it possible to study the dynamics of ventricular motion in a variety of clinical conditions.

Roentgenkymographic studies[3,5,10] have demonstrated that in patients with clinical and electrocardiographic evidence of myocardial infarction, anomalous motion of the wall of the left ventricle may occur and that it is similar to that described by Tennant and Wiggers[12] following the ligation of coronary arteries in dogs. These investigators observed on myographs recorded from the myocardium supplied by the ligated anterior descending branch of the left coronary artery " . . . a series of evoluting changes in contour of the contraction curve leading in about a minute to its complete inversion during systolic ejection."

During the 3 year period in which the electrokymograph has been available for the clinical investigation of heart disease, anomalous motion of the left ventricular wall[2,6] has been observed in patients showing definite clinical and electrocardiographic evidence of myocardial infarction. Previous reports of electrokymographic studies[2,6] of ventricular motion have merely mentioned anomalous motion of the left ventricle in cases of myocardial infarction. More recently anomalous motion of the wall of the right ventricle has been observed.

This report presents the electrokymographic observations of left ventricular motion in 48 patients having in common the complaint of precordial distress; and also presents the clinical diagnoses of a group of 18 patients who had abnormal electrokymograms of the right ventricle.

The Electrokymograph. The electrokymograph is an instrument designed to record motion of or changes in density of organs by recording variations in the intensity of a small Roentgen-ray beam. The technical aspects of the electrokymograph as well as its application have been adequately described in the literature[8,9]. Briefly, however, it consists of 3 essential parts, namely, a fluoroscope, a pick-up unit and a recording instrument.

The fluoroscope and the recording instrument (an electrocardiographic apparatus of standard design) require no special descrip-

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tion. The pick-up unit consists of a multiplier photo-tube (R.C.A.-931-A) with fluorescent material covering its photosensitive surface, a power pack for energizing the photo-tube and a filter-control unit for leading the current from the photo-tube across the galvanometer of the recording apparatus.

The multiplier photo-tube with its fluorescent covering is mounted between the patient and the fluoroscopic screen. Using the fluoroscopic screen, the photo-tube is positioned so that the center of its photosensitive surface is opposite the border of the heart. When the heart border moves laterally, as it does in diastole, more of the heart lies between the sensitive surface and the beam of Roentgen rays thus reducing the intensity of rays reaching this surface. This produces an upward deflection of the line. Conversely, in systole, with less of the heart between the sensitive surface and the Roentgen tube, more rays reach the phototube and the line moves downward.

To permit identification of the phases of the cardiac cycle on the electrokymogram (Eky), the carotid pulse is simultaneously registered on the same record, using a pressure cup fastened on the patient's neck over the carotid artery.

The curve of the carotid pulse provides 2 landmarks for identifying the phases of the cardiac cycle in the Eky[1,2]. The foot of the major ascending limb of the carotid pulse marks the beginning of the systolic ejection phase. The tip of the dicrotic notch on the descending limb indicates the closure of the semilunar valves.

With the carotid pulse recorder, correction factors must be used to allow for pulse transmission time and for the lag in air conduction as compared to the electrical conduction of the electrokymograph. The lag of the air conduction system has been determined as 0.01 seconds. The pulse transmission time from the left ventricle to the carotid artery is determined by comparing the timing of the pulse wave of the ascending aorta with the curve of the carotid pulse. When the carotid is used to identify right ventricular events, then corrections are determined by comparing the time relationships of the simultaneously recorded pulmonary artery electrokymogram (Eky) and the carotid pulse[1,2,4]. The accuracy of the determination based upon the carotid pulse is in the order of plus or minus 0.01 seconds.

Since adequate descriptions appear in the literature[1,2] concerning the interpretation of normal Ekys, only brief mention will be made here concerning the salient features of the Eky of the normal ventricle (Figs. 1, 2-A and 5-A). The Eky of the ventricle is found to have a striking similarity in general configuration to volumetric curves[1,2,14] of the ventricles obtained by direct cardiometer studies in animal experimentation. Tracings of both right and left ventricles in normal individuals show the same general pattern (Fig. 1): at the onset of systolic ejection as indicated by the opening of the semilunar valves (determined by projection from the pulse wave of the carotid artery) the curve (Eky) describing the motion of the ventricular border under examination is at or near the most lateral extent of motion (Fig. 1-point 2; top of the record). From this point the curve moves laterally for a brief period of time (approximately 0.04 secs.), then sharply medialward, the rapidity of its descent slowing as it reaches the most medial extent of motion (Fig. 1-point 3; bottom of record). Point 3 of Fig. 1 marks the closure of the semilunar valves and is determined by corrected projection from the dicrotic notch of the carotid pulse. Point 3 also marks the onset of isometric relaxation which is indicated on the Eky curve as a small secondary wave. Beginning at point 4 in Fig. 1 the curve ascends, following the lateral motion of the ventricular wall associated with diastolic filling. The diastolic component of the curve ends at point 5 and is followed by another small secondary wave (Fig. 1—1 to 2) which is associated with isometric contraction. This description of the normal ventricular Eky has been confirmed by Boone *et al.*[2] in 500 Eky examinations of 140 medical students and nurses whose cardiovascular systems were regarded as normal.

Routinely, the following positions are taken in the Eky examination of the left ventricular wall: in the anterior-posterior projection, motion is recorded from the upper (AP-ULV), the middle (AP-MLV), and the lower (AP-LLV) thirds of the left ventricular border; in the left anterior oblique position at approximately 20° to 30° at about the junction of the lower and middle thirds of the left ventricle (LAO-MLV); in the right anterior oblique position at approximately 10° to 20° midway between the pulmonary artery and the apex (RAO-MLV); in the left lateral projection on inspiration at a point just clear of the diaphragm (LL-MLV). With these positions the anterior, antero-lateral, postero-lateral and posterior portions of the left ventricle may be explored. Tracings taken at AP-ULV frequently have pulmonary artery and, or, auricular motion superimposed. Tracings taken at the position LL-

MLV are not always free from interference by the aorta or left auricle. Consequently for purposes of this study, these latter two positions are not reported.

The wall of the right ventricle is studied in the following positions: the lower right border (LRB) and the middle right border (MRB) of the heart in the anterior-posterior projection and the lower right border in the left anterior oblique position of 30° to 45° (LAO-LRB). Position LRB in the majority of individuals studied reflects motion predominantly of the right ventricle, whereas position MRB reflects motion predominantly

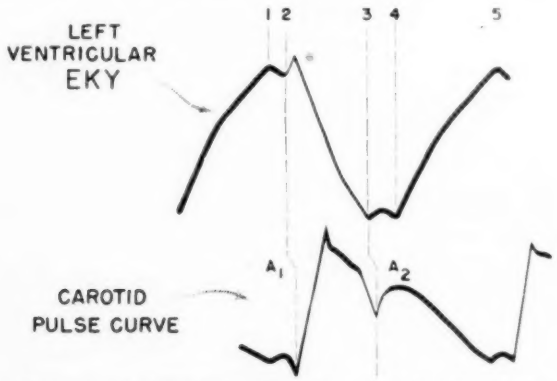

FIG. 1. Schematic diagram of electrokymogram from the border of the left ventricle and carotid pulse. One to 2 is isometric contraction; 2 to 3 systolic ejection limb (from opening of semilunar valves as determined by projection from the onset of the major ascending limb of the carotid pulse curve with correction A_1 for difference in air conduction versus electrical conduction and pulse transmission time to closure of semilunar valves as determined by corrected projection, A_2, from the dicrotic notch of the carotid pulse curve); 3 to 4 is isometric relaxation; 4 to 5 is diastolic filling period.

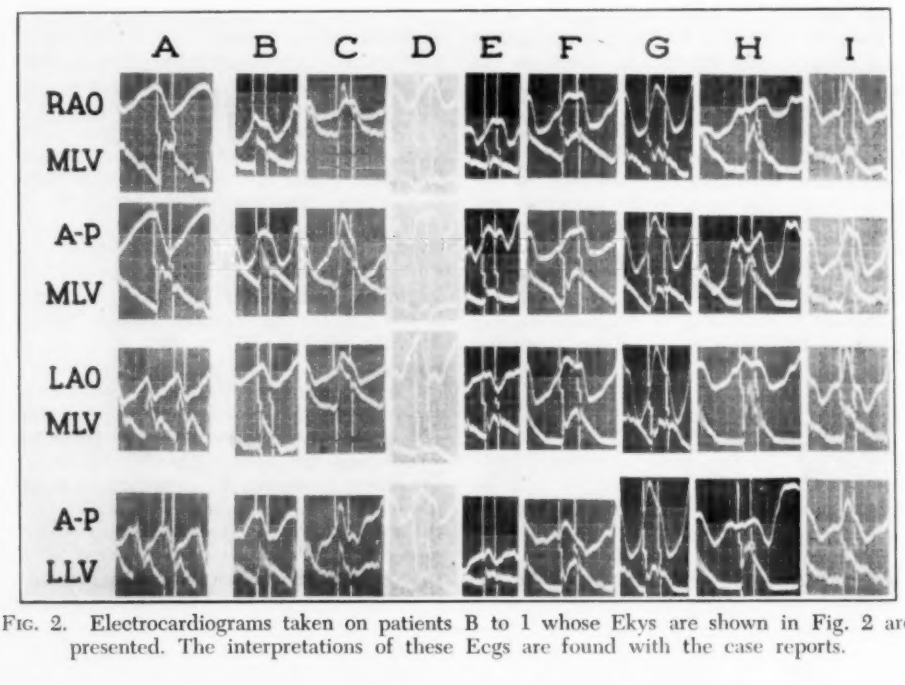

FIG. 2. Electrocardiograms taken on patients B to 1 whose Ekys are shown in Fig. 2 are presented. The interpretations of these Ecgs are found with the case reports.

of the right auricle[1,2]. Position MRB is included in the positions for study of right ventricular motion in order to determine grossly the extent of participation of the right auricle in the curve obtained from position LRB. Position LAO-LRB forms a countercheck for the right ventricular predominance of the curve in position LRB. Also in conjunction with the study of the wall of the right ventricle pulsations of the pulmonary artery along the left border of the cardiac silhouette were recorded for purposes of timing events occurring in the right ventricle as previously mentioned.

ELECTROCARDIOGRAM*. In all cases reported an electrocardiogram taken on the same day or one taken within a reasonable period of time of the Eky examination is included.

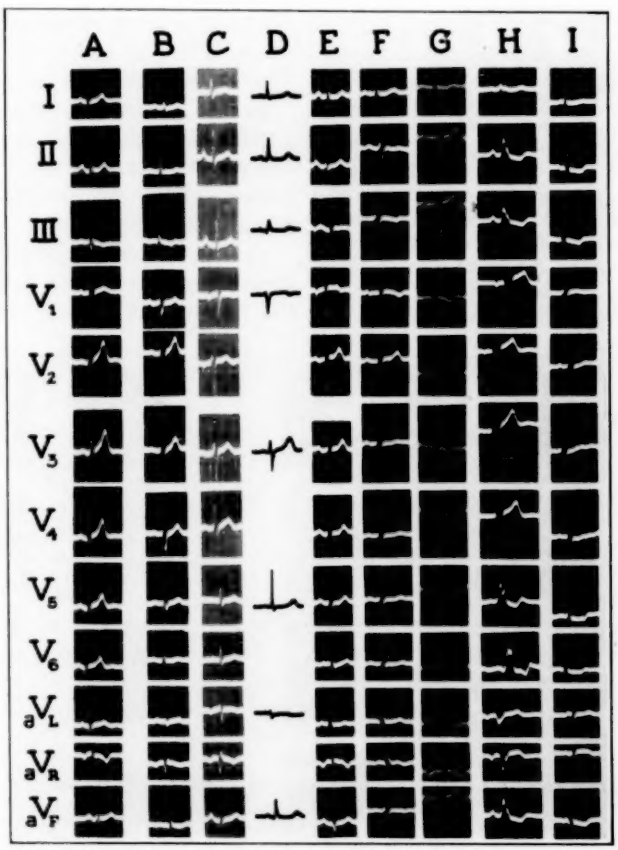

FIG. 3. Presentation of electrokymograms taken from the pulmonary artery and right ventricle on patients described under the right ventricle in the text. Pul. Art. = pulmonary artery Eky; A-P, LRB = anterior posterior projection lower third of the right border of the cardiac silhouette; LAO, LRB = left anterior oblique projection of from 30 to 45 degrees, lower third of the right border of the cardiac silhouette. The carotid pulse curve is below the Eky in each instance. Pulmonary artery is shown because it is used for determining the opening of the semilunar valves with the carotid pulse curve acting as the medium for this comparison as mentioned in the text. The first projection line from the carotid to the Eky marks the opening of the semilunar valves; the second indicates the closure of the semilunar valves. The interval between the 2 projection lines marks the systolic ejection phase of the cardiac cycle. A is the normal individual described under the left ventricle in the text.

* The authors are grateful to Dr. Maurice Sokolow for checking the electrocardiographic interpretations.

The Ecg for the left ventricular study included a minimum of the following leads: the 3 standard leads, the 3 augmented unipolar extremity leads of Goldberger[7] and the 6 (V_1 to V_6) precordial leads of Wilson[15]. In the study of the right ventricle the following leads are reported: the 3 standard leads, aV_L and aV_F and V_1, V_3 and V_5.

Clinical Material. *Left Ventricular Study.* Ekys and routine Ecgs were taken on 48 patients who were grouped into 4 classifications on the basis of clinical history and Ecgs as follows: 17 had had myocardial infarction; 18 patients had angina pectoris or coronary insufficiency; and a group of 13 miscellaneous patients who had as their common denominator precordial discomfort atypical for angina pectoris, coronary insufficiency, or myocardial infarction associated with other cardiovascular findings such as hypertension, marked arteriosclerosis, cardiovascular syphilis, abnormalities of rhythm, cardiac enlargement, or dyspnea on exertion.

In the study of the left ventricle, attention is chiefly focused upon this miscellaneous group with precordial discomfort and the group with established myocardial infarction.

Right Ventricular Study. During the course of the study of abnormal Ekys of the left ventricle, abnormal motion of the right ventricle was also detected. Accordingly, a group of 300 routine Ekys was studied in detail for evidence of abnormalities of right ventricular motion. Those found to have abnormal motion of the right ventricle were studied clinically and in so far as possible electrocardiographically.

Results. For the purposes of comparison an Eky and an Ecg from a subject with a normal cardiovascular system is included in Figs. 2, 3, 5, and 6 under the letter A.

The principal abnormalities of ventricular motion noted in the Ekys of the cases reported were as follows:

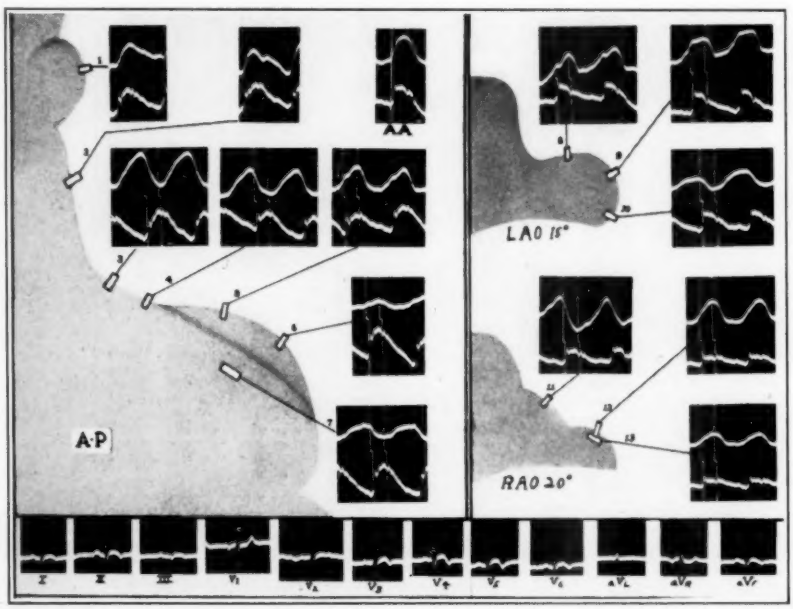

Fig. 4. Electrokymogram of the left border of cardiac silhouette in the anterior-posterior, the left anterior oblique, and the right anterior oblique projections from a patient having an aneurysmal dilatation along the lateral border of the left ventricle. Ecg accompanies the Eky. The Eky is above the carotid pulse wave in each position. Position AA is from the ascending aorta; 1 is at the aortic knob; 2 is at the pulmonary artery; 3, 4, and 11 are from the upper third of the left ventricle; 5, 6, 8, 9, 12 are over the aneurysmal area of the left ventricle; 10 is from the lower third of the left ventricle near the apex; 7 and 13 are Eky densograms taken through the left ventricle medial to the aneurysmal dilatation and directly through it respectively. More detailed information is found in the text.

during isometric contraction, marked lateral motion instead of a relatively short thrust of variable direction; during systolic ejection one of the following types of motion are found: 1, marked lateral motion of the ventricular wall of over 0.04 secs. duration followed by reduced medial or relatively no motion; 2, relatively absent motion; or 3, greatly reduced motion instead of a short lateral followed by a rapid medial motion as normally occurs; during the first third to half of the diastolic filling period medial motion was present instead of lateral motion throughout. (An Eky was regarded as questionably abnormal when its deviation from normal ventricular motion as described previously was marked and was in the direction of the type described as abnormal.)

In the miscellaneous group of 13 patients in whom the diagnosis of angina pectoris, coronary insufficiency, or myocardial infarction could not be established, the following is reported: 10 had abnormal Ekys; 3 were questionably abnormal.

Of 10 patients who had abnormal Ekys, 5 had Ecgs which were interpreted as borderline or as abnormal, but of no characteristic pattern and 5 were reported as within normal limits.

Of the 3 patients with questionably abnormal Ekys, 2 showed borderline or suspicious Ecgs and 1 was reported as normal.

The Ekys and Ecgs of 3 of these patients are presented in Figs. 2 and

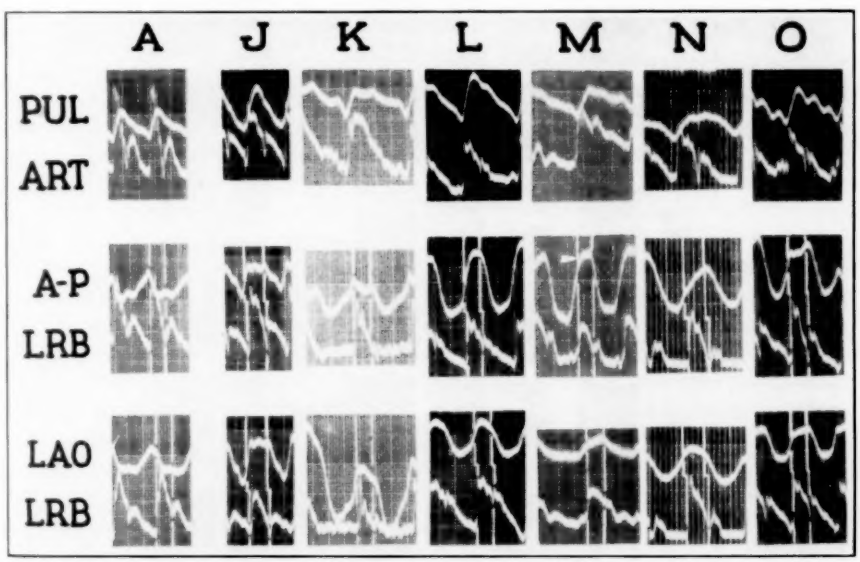

FIG. 5. Electrokymograms from the border of the left ventricle in the following positions and projections: mid left ventricle in the right anterior oblique, 10 to 20 degrees; mid left ventricle in the anterior-posterior projection; mid left ventricle in the left anterior oblique of 30 degrees; lower left ventricle in the anterior-posterior projection. A represents the Ekys from the normal. Detailed explanation of these curves is found in the case reports (Patients B to I). The carotid sphygmograms are below the Ekys. The projection from the carotid to the Eky is indicated in white; the jog in the projection line indicates the correction factor for air conduction and pulse transmission time. The first line indicates the opening of the semilunar valves, the second line the closure of the semilunar valves; the interval between the 2 lines represents systolic ejection.

3—B, C, and D. A brief summary of their case histories as well as the reports of their Ecgs and Ekys are presented in the case histories below.

In the group of 18 patients thought to have coronary insufficiency or angina pectoris, there were 11 abnormal Ekys of the left ventricle and 3 questionably abnormal. Of the 11 patients with abnormal Ekys, 4 had abnormal Ecgs, 3 had borderline Ecgs, and 4 were reported as within normal limits. (The authors recognize the importance of this group of patients and it is their intention to make a more detailed report of Eky findings in angina pectoris and in coronary insufficiency in the future.) Cases E and F are representative of this group. Their Ekys and Ecgs are shown in Figs. 2 and 3; the summaries of the case histories as well as the Eky and Ecg reports are to be found in the appendix.

Since the 17 patients who had myocardial infarction were chosen on the basis of clinical and electrocardiographic evidence of infarction, only the electrokymographic results are presented. Ten of these patients had abnormal Ekys of the left ventricle, in 6 the Eky was questionably abnormal, and in 1 it was normal. Cases G, H, and I in Figs. 2 and 3 show the Ekys and Ecgs on 3 patients of this group. The case history and reports of the Ecg

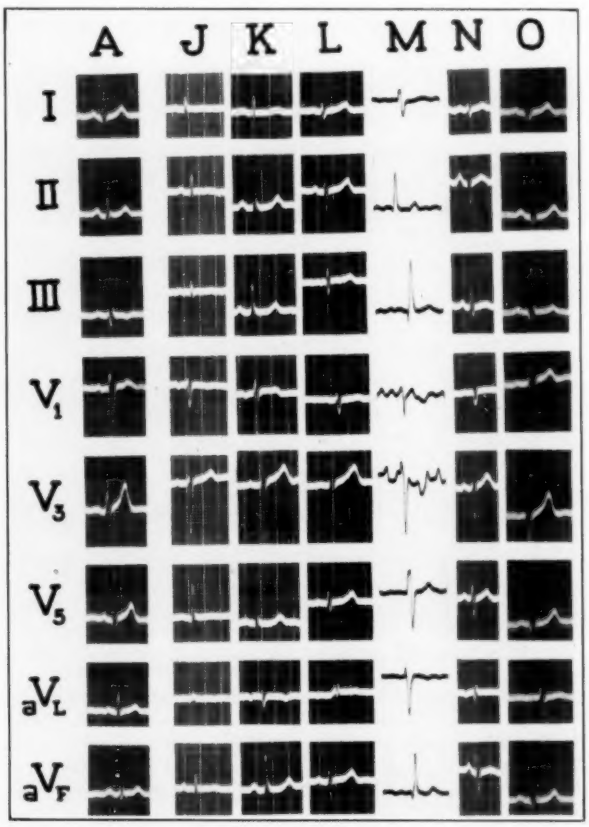

FIG. 6. The electrocardiograms taken on patients whose Ecgs are shown in Fig. 5 are presented. The interpretations are found with the Case Reports.

and Eky on Case H are included in the case histories below.

One of the patients (C. H.) in this series of myocardial infarctions was found to have a readily observed aneurysm of the ventricular wall by fluoroscopy. The diagnosis of post-infarctional aneurysm was corroborated by diodrast studies. Fig. 4 shows a sketch of the left border of the patient's cardiac silhouette as seen at fluoroscopy together with his Eky and Ecg. It is of interest to note in Fig. 4 that positions 5, 6, 8, 9, and 12 are taken over the aneurysm and positions 3, 4, 10, and 11 are superior and inferior to it. Position 13 is a density Eky of the aneurysm and position 7 is through the ventricle medial to the aneurysm. The positions taken over the border of and through the aneurysm show the Eky and the carotid wave traveling in the same direction; the remaining positions over the left ventricle grossly resemble those obtained from the normal left ventricle as illustrated in Fig. 1 and Fig. 2-A.

Right Ventricle. In a series of 300 routine Eky examinations made consecutively, abnormal motion of the right ventricle was found in a total of 18 patients and questionable abnormal motion was found in an additional 7 patients. For the purposes of this report the significant clinical findings for the 18 patients with definitely abnormal Ekys of the right ventricle are reported.

Eight patients had findings consistent with pulmonary disease as follows: bronchitis of unspecified etiology and asthma in 4; pulmonary emphysema in 2; pulmonary silicosis in 1; and in 1 lupus erythematosus disseminatus with involvement of lungs, pericardium and myocardium.

Seven patients had cardiac lesions as follows: 3 with rheumatic heart disease; 1 with a left ventricular aneurysm; 1 with angina pectoris; 1 with a patent ductus arteriosus; and 1 with an interventricular septal defect.

The complaints and clinical findings of the remaining 3 patients were vague and to date no diagnosis has been possible.

The Ekys and Ecgs of 5 of this group of patients are presented in Figs. 5 and 6—Cases J, K, L, M, N, and O. The diagnosis of each case is as follows:

Case J: A 17 year old male with lupus erythematosus disseminatus.

Case K: A 50 year old male with marked pulmonary silicosis.

Case L: A 17 year old female with a patent ductus arteriosus. Ecg was within normal limits.

Case M: A 28 year old male with mitral insufficiency, auricular fibrillation and marked cardiac enlargement.

Case N: A 32 year old female with asthma of undetermined etiology. Ecg was reported as borderline.

Case O: A 26 year old male with no tangible diagnosis but with the principal complaint of palpitation. Ecg was reported as within normal limits.

The Case Histories and the reports of the Ecgs and Ekys of Patients *J* and *K* are summarized in the appendix. The autopsy report on Patient *J* is summarized with his history.

It is of considerable interest to note that in 3 of the patients having abnormal motion of the right ventricle, abnormal motion of the left ventricle also occurred. These 3 patients had the following conditions; the first had chronic bronchitis of unknown etiology, asthma of unknown etiology, and angina pectoris; the second was the patient presented in Fig. 3 who had a large left ventricular aneurysm; the third, was a patient who had marked emphysema and precordial pain not typical of angina pectoris.

Discussion. In a group of 48 subjects having the complaint of precordial discomfort with other subjective and, or,

objective symptoms involving the cardiovascular system, abnormal Ekys of the wall of the left ventricle were observed in 31 (64%).

As this series of patients was not set up for statistical analysis, one can only observe that abnormal Eky motion of the left ventricular wall can occur in patients with evidence of myocardial infarction as well as in patients having complaints referrable to the heart without definite evidence of myocardial infarction. Conversely in such patients the Eky may present the accepted normal configuration for left ventricular motion. To date the authors have not observed the type of abnormal motion herein described in individuals who have had cardiovascular systems above suspicion.

Thus far, the authors have observed this type of abnormal Eky in 3 patients who had cardiovascular disease but without the symptom of precordial distress.

In the normal Eky[1,2] a curve is described which closely resembles in direction and general configuration, the classical ventricular volume curve[14]. That is, in systole the general direction of motion is medial and during diastole it is lateral. On the other hand, in the abnormal Ekys which have been described, the general direction of motion tends towards the opposite, that is, during systole—especially early systole—lateral motion becomes prominent and medial motion is largely diastolic, thus bearing a greater resemblance to a ventricular pressure curve[14] than to the volume curve. The curves in Fig. 4 show this difference in direction and configuration between the positions examined over the aneurysm as compared to other areas of the left ventricle.

The curves described bear a great resemblance to those obtained by Tennant and Wiggers[12] from the ischemic myocardium of the dog. They also bear a marked resemblance to the motion of the left ventricle as observed by roentgenkymography[3,5,10] in cases of myocardial infarction. Previous reports[2,6] as well as the reports on Cases G, H. and I above show this same abnormality of motion of the wall of the left ventricle in cases with evidence of myocardial infarction.

It is of interest to note in the roentgenkymographic studies referred to above that Dack *et al.*[3,10] reported 28 abnormal kymograms with negative Ecgs in a series of 200 cases and Garland and Thomas[5] report 10 with negative Ecgs in a series of 58 abnormal kymograms. Of 8 patients studied at autopsy from the series of Dack *et al.*, 6 were found to have evidence of infarction and 2 showed coronary sclerosis and myofibrosis with no evidence of infarction. All 8 had abnormal Ecgs and roentgenkymograms.

On the basis of the clinical histories and the Ecg findings, the abnormalities of the Ekys on Cases B, C, and D cannot be attributed to myocardial infarction without reservation.

Abnormalities of motion of the wall of the right ventricle as observed above have not been previously reported. The striking correlation of clinical evidence for some interference with the pulmonary circulation and the abnormalities noted on the Eky are of considerable interest.

While the explanation of these observations is not entirely understood, it would seem logical to ascribe the cause of these phenomena to something besides myocardial infarction and to search for a common denominator in the functional and, or, organic status of the ventricular wall relative to its elastic and contractile properties. The findings of Tennant and Wiggers[12] and Tennant[11] as the result of their perfusion experiments and the autopsy

findings in Patient *J* above provides one with ample reason to explore this field extensively.

The following explanation is offered: the myocardium of the ventricular wall is unable to overcome the load placed upon it as effectively as normal due to some deficiency in its elastic and, or, contractile properties. And further, the burden for the cardiac output may then principally rest on the piston-like action of the interventricular and auriculo-ventricular septae with the walls acting to a greater or lesser extent as passive retainers. The validity of this explanation will depend upon further study in this field as well as simultaneous studies of cardiac output combined with studies of septal activities along the lines reported by Westermark[13].

Case History Summaries. *Patient B.* (F.C.)—male; age 58; ht.: 173 cm.; wt.: 78.2 kg. On 3/1/48 he sought medical care because of shortness of breath on slight exertion and occasional precordial stabbing pain of momentary duration on exertion. These complaints have been present since 1939. Examination revealed moderate sclerosis of retinal vessels; B. P. 125/85; crepitant and musical rales in both lung bases posteriorly; increased resonance throughout chest; RBC 6.13 million; hemoglobin 17.4 gm. Roentgen-ray of thorax: enlargement of the pulmonary artery at the hilum and marked emphysema. *Electrocardiogram* 4/30/48 (Fig. 3-B): sinus rhythm, rate 90; P-R 0.18; QRS 0.09; axis +80; semi-vertical heart; low to flat T waves in II and V_6; diphasic T in aVF. Borderline record. *Electrokymogram* 4/30/48 (Fig. 2-B): positions RAO-MLV and AP-MLV show reduced motion during systole and medial motion during early diastole. Positions LAO-MLV and AP-MLV are grossly of normal configuration. (Motion of right ventricle and abnormal.)

Patient C. (R. J.)—male; age 37; ht.: 178 cm.; wt.: 65.9 kg. On 11/3/47 he sought medical attention for the complaint of intermittent precordial pain which had a duration of a few seconds to several hours. This complaint was present for past 2 years. It occurred with emotional and physical stress and was accompanied by shortness of breath. He is occasionally aware of his heart "pounding." Physical examination was negative. B. P. 130/88. Fluoroscopic examination of thorax revealed no recognized abnormalities of the heart and lungs. *Electrocardiogram* 11/4/47 (Fig. 3-C): sinus rhythm, rate 84; P-R 0.17; QRS 0.08; axis +77. Vertical heart. Record within normal limits. *Electrokymogram* 11/4/47 (Fig. 4-C): lateral motion during first half of systolic ejection in all positions on left ventricle with absent or reduced motion during latter one-half of systolic ejection in RAO-MLV and LAO-MLV with relatively sharp medial motion in latter one-half of systole in AP-MLV and AP-LLV. Early diastolic motion is chiefly medial.

Patient D. (O.B.)—female; age 62; ht.: 157.7 cm.; wt.: 58.7 kg. On 12/2/47 sought medical attention for boring pain left epigastrium with radiation to left lower precordium. Brought on with physical exertion and emotional tension. Noted since August, 1947. Physical examination revealed a rough systolic murmur at the apex with transmission towards the axilla. B. P. 125/75; hemoglobin 55%; RBC 3.5 million; no other tangible findings. Fluoroscopy of thorax: no abnormalities were noted. *Electrocardiogram* 12/1/47 (Fig. 3-D): sinus rhythm, rate 84; P-R 0.13; QRS 0.07; axis +45; semi-horizontal S-T segment in 2 and aVF is suspicious; otherwise, record appears normal. *Electrokymogram* 12/1/47 (Fig. 2-D): lateral motion in early systole followed by absent motion in RAO-MLV; continuing slow lateral motion in AP-MLV; and reduced medial motion in AP-LLV. Motion in position LAO-MLV corresponds to normal configuration.

Patient E. (S.W.—U121692)—female; age 72; ht.: 134 cm.; wt.: 71.8 kg. Developed complaint of precordial pain associated with exertion and excitement in 1945. No radiation of pain. Duration 15 to 30 minutes. Dyspnea accompanies pain. Pain is relieved by rest. These complaints have persisted until present examination on 6/16/48. Physical examination revealed enlargement of cardiac dullness to left of mid-clavicular line. B. P. 150/85; moderate generalized arteriosclerosis; no adventitious heart sounds. Roentgen-ray of chest on 10/24/45 and fluoroscopic examination on 6/16/48 revealed slight enlargement of the cardiac silhouette to the left with dilatation of the ascending aorta. *Electrocardiogram* (10/16/45) was interpreted as an abnormal record of no characteristic pattern suggesting myocardial disease. *Electrocardiogram* 6/16/48 (Fig. 3-E): revealed a rate of 100; P-R 0.20; QRS 0.07; axis −40. T of ½ mm. with R of 7 mm. in aVL; QS in aVF which may be positional. Horizontal

heart. Record was reported as probably within normal limits. *Electrokymogram* 6/16/48 (Fig. 2-E): lateral motion during first half of systole followed by reduced medial motion in positions RAO-MLV and AP-MLV. Early diastolic motion is chiefly medial. Motion in positions LAO-MLV and AP-LLV grossly follow normal patterns.

Patient F. (F.W.—U135542)—female; age 62; ht.: 157.5 cm.; wt.: 49.2 kg. Entered the University of California Hospital Clinic 12/11/46 for the complaint of diabetes known for 18 years and aching pain in left chest of 10 years' duration. Chest pain was precipitated by both exertion and emotion. Duration was a few seconds; disappeared at rest. It was accompanied by palpitation. No dyspnea. Diagnosis at this time was diabetes mellitus with moderate generalized arteriosclerosis and anginal syndrome. B. P. 120/70. Her diabetes was brought under control and her general condition improved; however, the precordial distress persisted until the present examination. On 6/8/48 her blood pressure was 150/80. No significant cardiac findings were noted on physical examination. Roentgen-ray of chest (5/4/48) revealed the transverse diameter of the heart as 14% above the theoretical normal according to the Ungerleider tables. Otherwise, no other cardiac abnormalities were noted. *Electrocardiogram* 6/25/48 (Fig. 3-F): sinus rhythm, rate 62; P-R 0.18; QRS 0.10; axis −20. Horizontal heart. Low voltage in unipolar leads with low to flat T waves in II, V_3 to V_6. The conclusion was: abnormal record of no characteristic pattern. Electrocardiograms taken on 12/12/46 and 5/4/48 were similarly interpreted. *Electrokymogram* 6/25/48 (Fig. 4-F): marked lateral motion during early systolic ejection followed by absent motion in RAO-MLV; continuing slow lateral motion in AP-MLV; reduced medial motion in LAO-MLV; and medial motion of greater rapidity in AP-LLV than in LAO-MLV.

Patient H. (J.M.—U95995)—male; age 60; ht.: 161.5 cm.; wt.: 48.5 kg. Entered the University of California Hospital Clinic in 1945 complaining of leg weakness on walking and rest pain in his calves. His condition was diagnosed as generalized arteriosclerosis with intermittent claudication. On 7/17/47 he returned to the Clinic complaining of a sensation of "pushing up" against his heart on arising from bed. This sensation radiated to his neck, jaw, and down the inner aspect of his left arm. Both leg and precordial distress could be precipitated by walking 100 yards. Noted dyspnea after eating. Cardiovascular examination revealed advanced arteriosclerotic changes in the fundi; blood pressure 120/75; accentuated A_2; absent dorsalis pedis arterial pulsations; feeble posterior tibial pulsations. Ecg. revealed an abnormal record characteristic of left bundle-branch block. Roentgen-ray of heart revealed the transverse diameter of the heart as 15% greater than the expected according to the Ungerleider tables and a calcified plaque in the aortic knob. On 5/24/48 he entered the Clinic with a history of having been hospitalized two weeks previously because of the onset of severe dyspnea and anterior chest pain which radiated down the left arm. The pain was not brought under control for a period of about 2 hours. Physical examination at this time revealed B. P. 110/65 and no significant changes since the previous examination. Essentially the Ecg. was the same; however, the transverse diameter of the heart by Roentgen-ray had increased from 15% to 40% greater than the expected by the Ungerleider tables. Roentgen-rays also showed a more marked rounding and prominent left heart border. It was felt that he had a myocardial infarction. *Electrocardiogram* 5/24/48 (Fig. 3-H): sinus rhythm, rate 65; P-R 0.17; QRS 0.14; axis +75. Vertical heart. Wide QRS complexes in all leads with depressed S-T segment in II, III, V_5, V_6, and aVF. Diphasic T in II, III, V_5, V_6 and aVF. Conclusion: abnormal record characteristic of left bundle-branch block. *Electrokymograms* 6/23/48 (Fig. 2-H): motion undulating but slight in all positions during systolic ejection phase. Pulmonary artery Eky (not shown on figure) leads the carotid pulse wave by 0.06 seconds, thus corroborating the electrocardiographic finding of left bundle-branch block.

Patient J. (P.G.—U140991)—male; age 16; ht.: 160 cm.; wt.: 44.4 kg. Was referred to the University of California Hospital Clinic on 5/16/47 because of pain in the great toe on the right foot and a treatment resistant ulcer on the left small toe. His course was steadily worse and he died 5/30/48. During this period he was hospitalized on 3 occasions. Extensive studies were done. His cardiovascular complaints were principally pain in toes, feet, hands, fingers, calves, and on his last admission, chest pain. Symptoms were accompanied by febrile reactions and anorexia. The salient points on physical examination were: a bilateral macular eruption over both malar areas and bridge of nose; generalized adenopathy; inconstant pericardial friction rub; no heart murmurs; absent to questionable ulnar, dorsalis pedis and posterior tibial artery pulsations; cyanosis of right great toe and ulcer on left small toe which progressed

to gangrene and was amputated; B. P. remained at about 125/65; a terminal bronchopneumonia developed. Extensive laboratory procedures were carried out including pathological studies of vessel, muscle, and lymph gland tissue. A clinical diagnosis of lupus erythematosus disseminatus was made and substantiated by autopsy.

Autopsy findings in part were as follows: obliteration of both pleural cavities by a large number of soft, almost gelatinous adhesions; adhesive pericarditis; heart weighed 250 gm.; the heart muscle was pale red-brown in color and was somewhat softer than normal. No gross areas of scarring, fibrosis or infarction. The endocardium was smooth; there was slight beading in the region of the mitral valve and a slight verrucal formation along the line of closure; the valves appeared to have functioned well; left anterior descending coronary artery at one point shows a fairly large atheroma; otherwise the coronary arteries appeared to be free of degenerative changes. The lungs appeared congested; the amount of aerated tissue was severely decreased.

Microscopic examination of the heart was reported as follows: "In the region of the tricuspid valve the myocardium shows a tendency to loss of the cross striations and to be replaced by connective tissue. There are frequent foci of pus cells and often there are areas of necrosis in the muscle. Plasma cells and other chronic inflammatory cells predominate. Early calcification in the affected stroma is noted. The smaller arterioles show frequent arteritis with some associated phlebitis. There is hyaline degeneration with necrosis and hemorrhage from the vessels. The stroma is often very edematous. The valve is normal.

The remaining regions of the heart show a similar process which varies somewhat in intensity from area to area. There are areas of marked periarterial edema and fibrosis with fragmentation and swelling of the collagen stroma. The myocardial cells in these areas often show cloudy swelling. A marked chronic fibrinous pericarditis is noted with considerable edema present. This is quite marked on the right side of the heart as well with marked alterations in the architecture of the myocardial stroma and cells. Some areas of the pericardium show a pus cells response rather than a chronic reaction.

The valves in general are well formed with some edematous swelling of the stroma of the aortic valve.

The coronaries show some chronic inflammatory cells in the adventitial layer with edema. One area has an atheromatous plaque partially obstructing the lumen."

Roentgen-rays of chest (5/19/47 and 8/13/47): cardiac shadow and lung fields were reported as within normal limits. 11/29/47: the cardiac shadow was reported as markedly increased in size. A pericardial effusion was thought to be present. Increased broncho-vascular markings were noted in both lung fields together with thickening of the pleura. 5/15/48: a slight decrease in the size of the cardiac shadow was reported. The lung fields were reported as clear.

Ecgs (5/17/47): reported as consistent with but not diagnostic of rheumatic carditis. 5/23/47: reported as compatible with myocardial involvement and possibly pericarditis. 6/16/47: reported as "an abnormal record indicative of myocardial involvement". 7/24/47 and 8/12/47: reported as "within normal limits". 11/30/47 and 12/8/47: reported as "abnormal record compatible with pericarditis". 12/15/47, 12/22/47, 12/27/47 and 1/13/48: reported as abnormal record of no characteristic pattern. 4/1/48: reported as borderline record with changes toward normal.

Electrocardiogram 5/13/48 (Fig. 6-J): sinus rhythm, rate 107; P-R 0.17; QRS 0.08; axis +60. Semi-vertical heart. Low voltage in standard leads and aVL; low to flat T in I, II, III, V_1, V_5, aVL and aVF. Abnormal record of no characteristic pattern.

Electrokymogram 4/16/48 (Fig. 5-J): sharp lateral motion followed by almost no motion during the systolic ejection period in both positions on the right ventricle. The direction of early diastolic motion in the positions shown is medial. Motion of the left ventricular wall is normal in direction; however, secondary waves usually ascribed to positional changes are absent.

Patient K. (D.C.–U36317)–male; age 50; ht.: 158 cm.; wt.: 58 kg. Between the ages of 31 to 39, this patient was a hard rock miner. In 1941 he entered the hospital because of occlusive vascular disease of his lower extremities. S.T.S. was negative at that time and the lungs showed no pathological physical findings (Roentgen-ray examination of chest not done).

After having been treated in 1942-43 for lues the patient re-entered the University of California Hospital Clinic on 4/19/48 and was sent to the hospital on 5/20/48 because of pains in his right foot and fatiguability of the legs. Arteriograms showed narrowing of the lumen of the descending aorta below the umbilicus and occlusive vascular disease in the upper extremities. B. P. was 145/70.

Roentgen-ray 5/28/48 revealed numerous small rounded nodular densities of calcified appearance widespread throughout both lungs representing probably a rather advanced degree of silicosis. Cardiac shadow is somewhat elongated and narrowed but not otherwise remarkable.

Electrocardiogram 6/4/48 (Fig. 6-K): sinus rhythm, rate 83; P-R 0.18; QRS 0.07; axis +70. Semi-vertical heart. Relatively low T_1. Record within normal limits.

Electrokymogram 6/4/48 (Fig. 5-K): only slight medial motion noted during systolic ejection period in both positions. Early diastolic motion is medial.

Summary and Conclusions. Abnormal Electrokymograms (Ekys) from the wall of the left ventricle were observed in myocardial infarction, coronary insufficiency, angina pectoris, and in patients with symptoms atypical of angina pectoris. Abnormal Ekys can be obtained in the presence of normal and borderline routine Ecgs.

Normal Ekys in the positions studied can be obtained from the left ventricle of patients with myocardial infarction, angina pectoris and coronary insufficiency.

Abnormal Ekys can be obtained from the wall of the right ventricle.

Fifteen of the 18 patients with abnormal Ekys of the right ventricle had evidence of cardiac or pulmonary disease, or both.

Abnormal Ekys can be obtained from the wall of both ventricles in the same individual.

Additional investigation is necessary before the full clinical significance of these observations can be established.

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RUPTURE OF THE HEART FOLLOWING MYOCARDIAL INFARCTION: DATA FROM A SMALL HOSPITAL

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Because of 7 cases of rupture of the myocardium occurring in this hospital during 1948—a relatively large number for a small hospital—and because of the fact that anticoagulant therapy is practically routine in the treatment of myocardial infarction, we have studied the literature and our cases to determine the relationship, if any, between anticoagulant therapy and this pathological condition. Our data are being presented in the hope that they will stimulate further investigation of this problem by others. It is noteworthy that the 106 autopsies performed in this hospital during the first 6 months of 1949 included 10 instances of acute myocardial infarction without one ruptured myocardium, the treatment being unchanged. We intend to present further data in a subsequent report.

Review of the Literature. None of the reports regarding the use of the anticoagulant drugs in myocardial infarction has referred to rupture of the myocardium. Indeed, Blumgart and his co-workers[4] have presented evidence to show that the time of myocardial healing is the same with or without the anticoagulants.

Prior to Krumbhaar's classical paper in 1925[13], rupture of the myocardium was regarded as rare. Since then, however, the literature has contained a number of reports of this condition which is now recognized as a definite clinicopathological entity. The data obtained from the review of the literature are summarized in Table 1.

A summary of the literature reveals that myocardial rupture, traumatic cases excluded, is almost invariably secondary to myocardial infarction. This usually is an acute infarct, *i.e.*, less than 2 weeks old, there being but 3 cases reported in which the rupture was through an old, healed lesion.

Most authors agree that exertion is an important etiologic factor in myocardial rupture. This might be correlated with the high percentage of ruptured myocardiums found at routine autopsies in mental institutions. In the reports from these institutions, it is interesting to note that all of the ruptures were of acute infarcts and that none of the infarcts had been diagnosed antemortem.

The anticoagulant drugs are not mentioned. This is not strange, considering that all but a few of these articles appeared prior to their use.

Memorial Hospital Cases. The data regarding the 7 cases of myocardial rupture found at autopsy at this hospital during the past 10 years are sum-

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TABLE 1.—REPORTS ON MYOCARDIAL INFARCTIONS AND RUPTURES SINCE 1925.

	Number of Autopsies	Number of Infarctions	Percent of Infarctions	Remote			Recent			Total Ruptures		
				No.	Rupt.	P. C.	No.	Rupt.	P. C.	No.	P. C. Aut.	P. C. Inf.
Krumbhaar[12]	16,000									7	0.04	
Munich	13,000									7	0.05	
Leipzig	8,000									9	0.11	
De La Chapelle[5]	15,059									20	0.13	
Wolff & White[29]		23					23	0	0	0		0
Parkinson & Bedford[20]		83					51	5	9.8	5		6
Levine[14]		46								9		19.5
Beresford & Earl[23]	2,374							46		46	1.9	
Lisa & Ring[15]	942	100	10.6							0	0	0
Benson *et al*[24]	7,000				2			33		35	0.5	
Meakins & Eakin[18]	6,548	62	0.95							3	0.0005	4.8
Smith & Bartels[24]	6,000							7		7	0.001	
Stewart & Eaton*[22]	840									6	0.72	
Salzmann[21]	5,000									6	0.001	
Eppinger & Kennedy[8]		200								15		7.5
Selzer[23]		95					95	8		8		8.4
Applebaum & Nicholson[1]		150								9		6
Bean[2]		300								17		5.7
Mallory *et al*[16]		72								8		11.1
Martland[17]	2,000									42	2.1	
Edmondson & Hoxie[7]	25,000						865	72	8.3	72	0.29	
Friedman & White**[11]	2,967	270	9.1	165	0	0	105	10	9.5	10	0.34	3.7
Jetter & White*[13]	115	47	41.0	25	0	0	22	16	73.0	16	13.9	34.0
Segall[22]		49								3		6.1
Mintz & Katz[19]		46								8		17.4
Diaz-Rivera & Miller[6]	1,250	147	11.8	94	0	0	53	5	9.5	5	0.4	3.3
Wang *et al***[26]	7,018	580	8.3							23	0.33	3.9
Wartman & Hellerstein[27]	2,000	160	8.0	49	1	2.2	111	6	5.4	7	0.35	4.4
Yater *et al*[29]		137					84	3	3.6	3		2.2
Foord[9]	3,173	422	13.3	107	0	0	315	32	12.5	32	1.2	7.6
Memorial Hospital	933	78	8.3	27	0	0	51	7	13.7	7	0.75	8.9

* Mental ** Massachusetts General Hospital

TABLE 2.—DATA ON THE 7 CASES OF THIS STUDY.

Patient	Age	Sex	Time of Onset of Symptoms Before Death	Clinical Findings: Exertion	Hypertensive Cardiovascular Disease	E. C. G.	Digitalis	Fever	Tachycardia	Leucocytosis	Sed. Rate	Anticoagulant	Prothrombin Time Day of Death	Hypert. Left Vent.	Path.: Ant. or Post.	Recent
12459	67	F	6 D	−	+*	−	−	+	+			−		+	AP	+
11909	52	M	11 D	−	−	+	+	+	+	+	+	−			P	+
77150	67	F	29 H	−	+	+	−	−	+			+			A	+
77333	54	M	5 D	+	−	+	+	+	+	+	+	+	8 P. C.†		A	+
79979	74	F	3 D	−	−	+	+	+	+	+	+	+	Less than 6 P. C.		A	+
47685	81	F	29 H	−‡	−	+	−	−	+	+		−		−	P	+
80666	75	M	7 D	+	−	+	+	+	+	+	+	+	15 P. C.		A	+

* Systolic hypertension only.
† Received Vitamin K.
‡ Exertion at onset.

marized in Table 2. The series, while small, gives results in keeping with those in the literature. All ruptures occurred at the site of fresh infarction. Clinically, the time between the onset of symptoms of myocardial infarction and death of the patient varied between 29 hours and 11 days, an average of 5 days. The clinical findings regarding the age of the infarct were confirmed at autopsy. Two of the 7 occurred immediately following exertion, and 4 of the 7 were taking digitalis (Table 3). Four of the 7 had been given anticoagulants; this means 4 out of every 5 in 1948. The series is of course too small to support positive conclusions. Moreover, there is overlapping of possible causes in that 2 of those who were taking anticoagulants were among those who had undergone unusual exertion immediately prior to death.

TABLE 3.—RELATION OF EXERTION, DIGITALIS AND ANTICOAGULANTS TO RUPTURE.

	Exertion	*Digitalis*	*Anticoagulant*	*Total Ruptures*
1938–1947	0	1	0	2
1948	2	3	4	5
Total	2	4	4	7

Discussion. Foord's[9] recent report showed an incidence of myocardial rupture comparable to that of the present series. His cases, however, were spread out fairly evenly over a 17 year period[10].

Despite the small number of our cases, it is significant that 5 ruptures occurred in 1 year, the other 2 occurring during the remaining 9 years.

Conclusions. This series of 7 cases of myocardial rupture is reported because a significant number occurred in a small hospital during a single year (1948).

Myocardial rupture is most likely to occur during the first 2 weeks following an acute infarct. Keeping the patient at absolute bed rest during this period will minimize the danger of this complication.

While digitalis must be used in acute infarction when myocardial failure develops, this should be done with great caution and with the knowledge of its danger during this period.

Our data, together with those of Foord, suggest that the use of anticoagulant drugs does not predispose to myocardial rupture. Statistical analysis of a much larger series of cases is necessary, however; pending this, the possibility of such a relationship should be kept in mind.

The authors express their appreciation to the Staff Members of the Memorial Hospital for permission to include their private cases in this report.

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A NEW TEST FOR VASOPRESSOR SUBSTANCES IN HYPERTENSION

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Hypertension has been proved to be no simple condition. It may range from a benign to an extremely malignant form. The importance of nervous, renal, and adrenal factors contributing to the condition differs with the individual patient[7]. Experimental studies have led to the present day differentiation between essential or primary hypertension, and hypertension secondary to renal disease, both being the result of increased peripheral resistance. Malignant hypertension is probably similar to benign but of much more severe grade, leading to widespread degeneration and occlusion of peripheral vessels, though some look on it as qualitatively different.

The reason for the increased peripheral resistance has been ascribed by some to a reduction in the size of the vascular bed of the kidney; by others, to the retention within the circulation of a specific vasoconstrictor substance. This substance, called angiotonin or hypertensin, is believed to be the result of a renin activator (a serum globulin called angiotonin precursor or hypertensin precursor) upon renin (produced or stored in the epithelium of the proximal convoluted tubules). The precursor of the active substance is presumably produced in the liver, as it disappears from the blood after hepatectomy.

Other investigators have demonstrated the presence of additional powerful pressor substances in blood (Bing, Zucker, Raska, Holtz, and others)[1].

Epinephrine, histamine, adenylic acid, acetyl choline and choline found in normal animal tissue are capable, at high dilution, of effecting changes in the caliber of blood vessels. Serotonin is a vasoconstrictor which has been isolated from beef serum[8].

The periodical discharge of adrenalin into the blood stream occurs in adenoma of the adrenal medulla or of outlying chromaffin tissue (pheochromocytoma). The high blood pressure of pituitary basophilism is probably the result of adrenal stimulation[1].

The normal kidney contains an enzyme (angiotonase or hypertensinase) which inactivates the pressor principle, angiotonin.

The cause of hypertension in pregnancy is unknown. It may be "essential hypertension" or it may be evidence of toxemia. It appears that essential hypertension predisposes pregnant women to toxemia[6]. Plasma from eclampsia patients exerts an antidiuretic effect, increases urinary chlorides, and raises blood pressure when injected into rabbits[1].

The experiments of Goldblatt are well known, in which constriction of the renal artery produced hypertension[5].

Smithwick has described 3 factors (neurogenic, humoral and vascular) which appear to affect peripheral resistance in hypertensive patients[9].

In this article, a new test is presented for the detection of vasopressor substances in the blood serum of hypertensive patients.

Method of Determining Normal Circulation Time in Rabbits[2]. Young white female rabbits are used. The animal is placed in a Cornell animal box, with the head protruding. One cc. of 10%, or preferably ½ cc. of 20% sodium fluorescein is injected rapidly

into the marginal vein of the ear. With the left hand another person holds a small portable ultraviolet light plus filter (kept turned on throughout the test) and a stop watch. The right hand turns off the room light, *e.g.*, an ordinary lamp light. The ultraviolet light is directed toward the rabbit's eye, and the right hand is used to separate the rabbit's eyelids. The stop watch is stopped immediately upon noting a brilliant yellow color in the conjunctiva along the inner margin of the eyelids. Almost simultaneously there is a brilliant yellow color in the iris of the eye, the nostrils and the gums of the animal. The average normal circulation time in rabbits is 5 to 6 seconds[2].

Effect of Drugs on Circulation Time in Rabbits[3]. The normal circulation time was determined for each rabbit. The fluorescein method was used to determine blood velocity at various times after intravenous administration of drugs. In most instances, caffein, coramine, metrazol, and strychnine slightly decreased circulation time (increased blood velocity), while adrenalin, pituitrin, and to a lesser extent, neosynephrine hydrochloride and paredrine hydrobromide, lengthened circulation time.

TABLE 1.—EFFECT OF ADRENALIN ON THE CIRCULATION TIME IN THE RABBIT

Adrenalin (*minims*)	*Time Between Drug Injection and Circulation Time* (*minutes*)	*Circulation Time* (*seconds*)
1	1	9.4
1	1½	11.0
1	2	15.0
1	2½	11.4
1	3	8.4
1	5	8.0
5	1	43.0
5	1	59.0

TABLE 2.—EFFECT OF BLOOD FROM PERSONS WITH NORMAL BLOOD PRESSURE ON THE CIRCULATION TIME OF THE RABBIT

Name	*Sex*	*Color*	*Age*	*B. P.*	*Circulation Time (Rabbit)*
M. S.	F	W	59	100/70	4.4 sec.
E. S.	M	W	26	120/82	3.8 "
W. R.	M	W	28	116/80	5.0 "
D. K.	M	W	42	110/72	6.6 "
O. H.	M	B	55	132/80	8.2 " *
M. D.	M	W	60	138/86	4.0 "
B. B.	F	W	58	150/90	5.2 "
J. P.	M	W	58	120/56	6.6 "
R. B.	M	W	15	126/80	4.8 "
F. A.	F	W	48	150/80	17.0 " *
G. C.	M	W	54	100/68	6.0 "
W. K.	M	W	41	110/70	7.0 "
J. A.	M	W	53	110/80	6.0 "
J. R.	M	W	70	120/60	15.2 " *
M. F.	F	W	5	not taken	6.2 "
M. D.	F	B	20	118/70	6.4 "
E. A.	M	W	21	106/80	5.8 "
G. R.	F	W	22	124/90	5.6 "
J. E.	M	—	—	Normotensive Pernicious Anemia	5.0 " †

* Although individuals had normal blood pressures, their blood serums showed prolonged abnormal circulation times for the rabbit. In cases O. H. and J. R., rabbits were injected with hypertensive human serum for tests 3 weeks previously; Case F. A. had hypertensive serum 5 weeks previously. There may be a tolerance or changed sensitivity in the rabbit as a result of repeated injections of hypertensive human serum (tachyphylaxis).

† Indianapolis General Hospital cases: specimens of blood mailed to Philadelphia, courtesy Dr. K. G. Kohlstaedt, Director, Lilly Laboratory for Clinical Research.

In human beings, the opposite result occurs. The administration of adrenalin speeds up the circulation time.

In a white male patient, aged 50, with bronchial asthma, the following observations were made: B.P. 120/72. 3 cc. 10% Mag. Sulph. intravenously. Circulation time *12 seconds.*

Two minutes after injection of 13 minims adrenalin hypodermically, B.P. 184/100.

Three minutes after injection of above adrenalin, 3 cc. 10% Mag. Sulphate i.v. Circulation time *7 seconds.*

Fifteen minutes after injection of adrenalin, B.P. 128/68.

Fluorescein has also been used to determine circulation time in humans[4].

A New Test For Vasopressor Substances in the Blood of Hypertensive Patients. A rabbit is placed in a Cornell animal box; 3 cc. of human blood serum at room temperature are injected into the ear vein; 2 to 4 cc. may be used, with 2 cc. giving lower readings. After 2 minutes, the fluorescein circulation time is determined. The results are given in Tables 2, 3, 4 and 5.

Neither warm weather nor the passage of several days' time between withdrawal of blood from the person and its injection into the rabbit interfere with the test.

Four specimens of blood serum were sent from Indianapolis General Hospital marked Code No. 1, 2, 3, 4.

Code 1. 4 cc. Serum—Circulation time 5.2 sec. (normal)

Code 2. 3 cc. Serum—Circulation time 4.0 sec. (normal)

Code 3. 4 cc. Serum—Circulation

TABLE 3.—EFFECT OF BENIGN HYPERTENSIVE BLOOD

Name	*Sex*	*Color*	*Age*	*Diagnosis*	*B. P.*	*Circulation Time (Rabbit)*
E. Z.	F	W	59	Benign Hypertension	230/100	15.8 sec.
R. M.	F	W	59	" "	180/100	13.6 "
B. C.	M	W	60	" "	206/134	23.2 "
A. K.	M	W	67	" "	210/120	4.0 " *
F. J.	M	B	49	" "	170/98	8.0 "
M. F.	F	W	61	" "	170/90	10.6 "
G. C.	F	W	49	" "	190/90	10.8 "
R. L.	F	W	74	" "	200/120	8.0 "
B. D.	M	W	54	" "	190/100	3.0 "
A. K.	M	W	67	" "	200/120	6.0 " *
D. B.	M	W	28	" "	140/50	10.0 "
W. G.	M	W	58	" "	202/96	5.0 "
J. M.	M	W	48	" "	162/90	7.8 "
A. K.	M	W	67	" "	248/124	5.8 " *
A. B.	F	W	63	" "	170/110	7.8 "
C. T.	F	W	66	" "	180/90	16.6 "
L. E.	F	W	72	" "	206/140	21.2 "
S. K.	F	W	56	" "	242/100	4.2 "
A. Y.	M	W	64	Uremia	180/90	8.8 "
M. M.	F	W	73	Benign Hypertension	170/110	8.2 "
A. M.	F	W	53	" "	160/70	10.2 "
E. U.	F	W	28	" "	162/100	9.2 "
H. C.	M	W	32	" "	190/100	8.8 "
S. P.	F	W	55	" "	230/120	12.0 "
A. W.	F	W	70	" "	240/120	17.4 "
J. C.	M	W	46	" "	210/160	13.8 "

* Same patient on 3 different days—note how similar results are, even though they are normal results in a hypertensive case.

time 11.4 sec. (abnormal). Increased vasopressor substances.

Code 4. 3 cc. Serum—Circulation time 13.0 sec. (abnormal). 1½ cc. Serum—Circulation time 8.8 sec. (abnormal). Increased vasopressor substances.

Later data were received on these cases.

Code 1. Normal blood pressure, pernicious anemia

Code 2. Normal blood pressure

Code 3. Male, white, age 42. Malignant Hypertension. B.P. 213/155. Blood Urea N. 44 mg/100 cc. Urea clearance 19% of average normal. Ophthalmoscopic examination reveals papilledema, numerous hemorrhages, exudates and intense vasoconstriction with marked arteriolar sclerosis.

Code 4. Male, white, age 52. Malignant Hypertension. B.P. 225/122. Blood Urea N. 54 mg/100 cc. Urea clearance 17% of average normal. Changes in the optic fundi indicative of the onset of malignant syndrome.§

Comment. Using fluorescein intravenously, the average normal circulation time in rabbits is 5 to 6 seconds. An arbitrary dividing line between normal and abnormal circulation time in rabbits *after* the injection of *human blood serum* may be taken as 7.5 seconds. Below 7.5 seconds can be regarded as normal and above 7.5 seconds as prolonged. The presence of excessive vasopressor substances in the blood serum of hypertensive patients probably causes a peripheral vasoconstriction in the rabbit, with a resulting prolonged circulation time.

Almost all persons with normal blood pressures yielded normal results. Whether those who gave abnormal results will later develop hypertension remains to be seen. Further studies to determine if potential hypertensives can be so diagnosed prior to clinical manifestations are indicated.

Most of the cases with hypertension, especially malignant hypertension, gave abnormal results. The few that did not may have been cases of very benign type; in the future it might be of value to correlate eye ground findings, etcetera. It is of interest to note that in the cases of hypertension with uremia, only a slight to moderate prolongation of circulation time occurred.

It would be interesting to measure the effect on rabbit circulation time of blood from a patient with proved pheochromocytoma. Corroborative diagnostic evidence might be secured if the time were markedly prolonged.

Various other conditions may prolong circulation time in rabbits. In one

TABLE 4.—EFFECT OF MALIGNANT HYPERTENSIVE BLOOD

Name	*Sex*	*Color*	*Age*	*Diagnosis*	*B. P.*	*Circulation Time (Rabbit)*
A. G.	F	W	43	Malignant Hypertension	240/140	14 0 sec.
F. H.	F	W	60	" " Uremia	240/130	8 2 "
E. S.	F	W	20	" " Uremia	190/140	9 2 "
E. B.	F	W	43	" "	250/120	8 4 "
B. H.	M	—	—	" "	— —	17 2 " *
I. C.	F	—	—	" "	— —	8 2 " *
	F	—	—	Eclampsia	150/90	14 0 " *

* Indianapolis General Hospital cases: specimens of blood mailed to Philadelphia, courtesy Dr. K. G. Kohlstaedt, Director, Lilly Laboratory for Clinical Research.

§ I wish to thank Dr. K. G. Kohlstaedt, Director, Lilly Laboratory for Clinical Research, for these cases.

experiment ice cold blood serum prolonged circulation time to 50.2 seconds, whereas the same serum at room temperature yielded a circulation time of 4.6 seconds.

If the patient has received certain drugs such as ergot, abnormal results may be obtained. Other drugs may cause the death of the rabbit.

It was intended to inject whole human liquid blood into a rabbit to note the effect on the circulation time. However, the rabbit may die if citrated or heparinized blood is used. Tubes with 10 cc. blood and 1 cc. of 1% sodium citrate in normal saline were prepared. Four cc. of blood from these were injected into each of 3 rabbits. Within a few minutes, 2 rabbits died; 1 animal became very sick but recovered. Four cc. of blood containing 3 drops of heparin were injected into 1 rabbit; the animal died within a few minutes. Another rabbit received 3 cc. of blood containing 1 drop of heparin, and no ill effects were observed. Two rabbits received 0.5 cc. of oxalated blood without any apparent ill effect, but since oxalated blood is probably toxic, larger quantities were not given. One half cc. of oxalated blood appears to be too small an amount for circulation time studies.

TABLE 5.—EFFECT OF PATIENT RECEIVING CERTAIN DRUGS ON RABBIT CIRCULATION TIME

Patient	*Sex*	*Age*	*B. P. before*	*B. P. after*	*Cause for hospitalization*	*Drug Received*	*Circulation Time*
T. S.	F	21	164/80	110/70	Obstetric delivery	Ergotrate 1/320 gr. T. I. D. 4 da.	41 2 sec.
E. K.	F	24	170/50	120/80	Obstetric delivery	Ergotrate 1/320 gr. T. I. D. 5 da.	55.8 sec.
J. C.	F	30	150/90	124/80	Obstetric delivery	Pituitrin and ergotrate	1 min. 13.2 sec.
E. H.	F	48	200/100			20 cc. chloral hydrate	2 cc. blood serum injected 55.4 sec. rabbit died

Summary. 1. A new test for vasopressor substances in the blood of hypertensive cases is presented, depending upon the injection of 3 cc. of human blood serum into the ear vein of a rabbit and the subsequent determination of the animal's circulation time by a fluorescein method.

2. Less than 7.5 seconds circulation time is judged to be normal; longer than that, abnormal.

3. Serum from hypertensive patients usually prolonged circulation time in the rabbit.

4. The increased circulation time was probably caused by the presence of excessive vasopressor substances in the blood serum from hypertensives.

5. Further studies are indicated to evaluate the test in diagnosis of prehypertension, benign hypertension, malignant hypertension, pheochromocytoma, prior to and after dorsolumbar sympathectomy for hypertension, and in the diagnosis of early eclampsia.

These studies were supported by a grant from the Jewish Hospital of Philadelphia Research Funds. I wish to thank Mrs. Gertrude Freedman, M.T., technician, for her valuable assistance, and Dr. and Mrs. Hugh Montgomery, for aid in editing this manuscript.

Portable Ultraviolet Lamp, with Wood's Filter, used most of the time, was a Model H Mineralight, weight 3 oz. The bulb is a short wave (2537 A.U.) ultraviolet lamp.

Another lamp used was a Spot Quartz lamp, with Wood's Filter, which is a mercury quartz low-temperature lamp, weight 54 oz. Its ultraviolet emission is almost completely (95%) in spectral band at 2540 Angstrom Units (A.U.).

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THE COINCIDENCE IN AUTOPSY MATERIAL OF NEPHROSCLEROSIS AND CARDIAC HYPERTROPHY WITH A CLINICAL HISTORY OF HYPERTENSION

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It is generally accepted that there is an association between hypertension, cardiac hypertrophy and nephrosclerosis, and one might therefore expect that a history of hypertension as well as anatomic findings of cardiac hypertrophy and arteriolar nephrosclerosis would, as a rule, be found together in patients coming to autopsy. However, experience with pathologic material suggests that the coexistence of all 3 factors is not the rule but the exception. Therefore, the numerical relationship of these factors together and in combination was studied in a large autopsy series in order to define the cases in which this coincidence is present or absent.

The extensive literature on the relationship among the 3 factors, arteriolar nephrosclerosis, cardiac hypertrophy and hypertension, points out that nephrosclerosis may result in hypertension[8] or hypertension and nephrosclerosis may cause cardiac hypertrophy[3,4,6,14]. Myocarditis is also accepted as a cause of cardiac enlargement[1,5,10,12,13,15]. Cardiac hypertrophy appears to be related to the severity rather than to the duration of the hypertension[16]. The reason for cardiac hypertrophy under such conditions has been widely discussed and is associated with myocardial fibrosis and, or, coronary sclerosis[7,9,10,11,12,15].

Material. The data utilized in this study were obtained from the autopsy protocols of 10,882 patients of Cook County Hospital from 1930 to 1939 inclusive. Of this group, all instances were selected in which one or more of the following 3 findings were recorded:

a. Blood pressure greater than 150/90. A blood pressure of 150/90 was taken to be the maximal normal value[17].

b. Heart weight above 500 gm. (later designated as Group A) or above 350 gm. (later designated as Group B). The heart weight is usually regarded as the best index of cardiac hypertrophy[7]. The weight regarded as definitely excessive cannot be clearly defined since it depends upon the size of the person, the sex, and also on the size of the portion of great vessels which may be left attached to the heart at the weighing. In the literature, a maximal heart weight of 364 gm. for males and 295 gm. for females has been recorded[2] with an average of 300 gm. for males and 250 gm. for females[15]. For a unified analysis, it was decided to consider hearts over 500 gm. (Group A) as definitely in the pathologic range, and hearts over 350 gm. (Group B) as possibly excessive.

c. Arteriolar nephrosclerosis as evidenced by standard gross and microscopic criteria. Changes resulting from arteriosclerosis without arteriolar involvement were not included.

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In this analysis all instances in which cardiac hypertrophy could have been attributed to pulmonary, valvular, myocarditic, pericarditic, hematologic alterations, or congenital abnormalities, were excluded. Instances of recent cerebral trauma, brain tumors, meningitis, and acute or chronic inflammatory renal disease were also omitted. Hearts with coronary sclerosis were included since the latter is known to be often combined with hypertension. This may represent a source of error in view of the known enlargement of the heart due to coronary sclerosis alone[5,9, 12,15]. Of the total number of autopsies surveyed, 1940 were found to be satisfactory for inclusion into Group A, and 2228 into Group B. A second source of error may result from the tabulation of a blood pressure below 150/90 at the time of admission or before death secondary to terminal cardiac failure.

Results. If 500 gm. (Group A) was taken as the lower limit of a hypertrophied heart, hypertension, cardiac hypertrophy, and nephrosclerosis were found in only one-fifth of the cases. If 350 gm. (Group B) was taken as the lower limit, hypertension, cardiac hypertrophy, and nephrosclerosis was found in one-third of the cases (Table 1). If combinations of only 2 factors were recorded they were found in about equal percentage, 34.9% in Group A and 34.4% in Group B. When only 1 of the 3 factors was recorded they totaled 42.5% in Group A and 32.3% in Group B (Table 1).

If the higher limit of heart weight is accepted, nephrosclerosis and hypertension appeared alone in about one-fifth of the cases. Cardiac hypertrophy alone was rare. In contrast to this, if the lower limit is accepted, cardiac hypertrophy alone was found in about one-fifth of the cases, whereas nephrosclerosis and hypertension were relatively rare (Table 1).

If blood pressure findings were disregarded, it was found that with the higher weight limit (Group A) more than one-half of the cases had nephrosclerosis alone and one-third had cardiac hypertrophy with nephrosclerosis while only 13.2% revealed cardiac hypertrophy alone (Fig. 1). If the lower limit of cardiac hypertrophy is accepted (Group B) cardiac hypertrophy alone becomes fairly common

TABLE 1.—PERCENTAGE INCIDENCE OF THE VARIOUS COMBINATIONS IN WHICH CARDIAC HYPERTROPHY, NEPHROSCLEROSIS, AND HYPERTENSION WERE FOUND IN THE AUTOPSY MATERIAL STUDIED

Combination of Factors Studied	*Percentage Distribution*		*Above 500 gm.*	*Above 350 gm.*		*Above 350 gm.*
Cardiac hypertrophy, nephrosclerosis, and hypertension	21.7			32.6		
Cardiac hypertrophy and hypertension	6.3			15.3		
Cardiac hypertrophy and nephrosclerosis	4.1	34.9		13.2	34.4	
Hypertension and nephrosclerosis	23.5			5.9		
Cardiac hypertrophy	5.4			17.9		
Nephrosclerosis	21.1	42.5		8.7	32.3	
Hypertension	17.3			5.7		
Total No. of Cases	1940			2228		

and almost half of the cases revealed cardiac hypertrophy and nephrosclerosis, whereas nephrosclerosis alone was only rarely recorded (Fig. 1). If, on the other hand, the nephrosclerosis was disregarded in Group A, hypertension was found alone in one-half of the cases, hypertrophy alone in only 12% of the cases, while hypertension with hypertrophy was seen in 35.8% of the cases. If the lower limit is accepted (Group B), these relations were radically changed in that hypertrophy was found associated with hypertension in one-half of the cases and hypertrophy alone in one-third. If one discounts the cardiac weight in this series, 64% of the cases had both nephrosclerosis and hy-

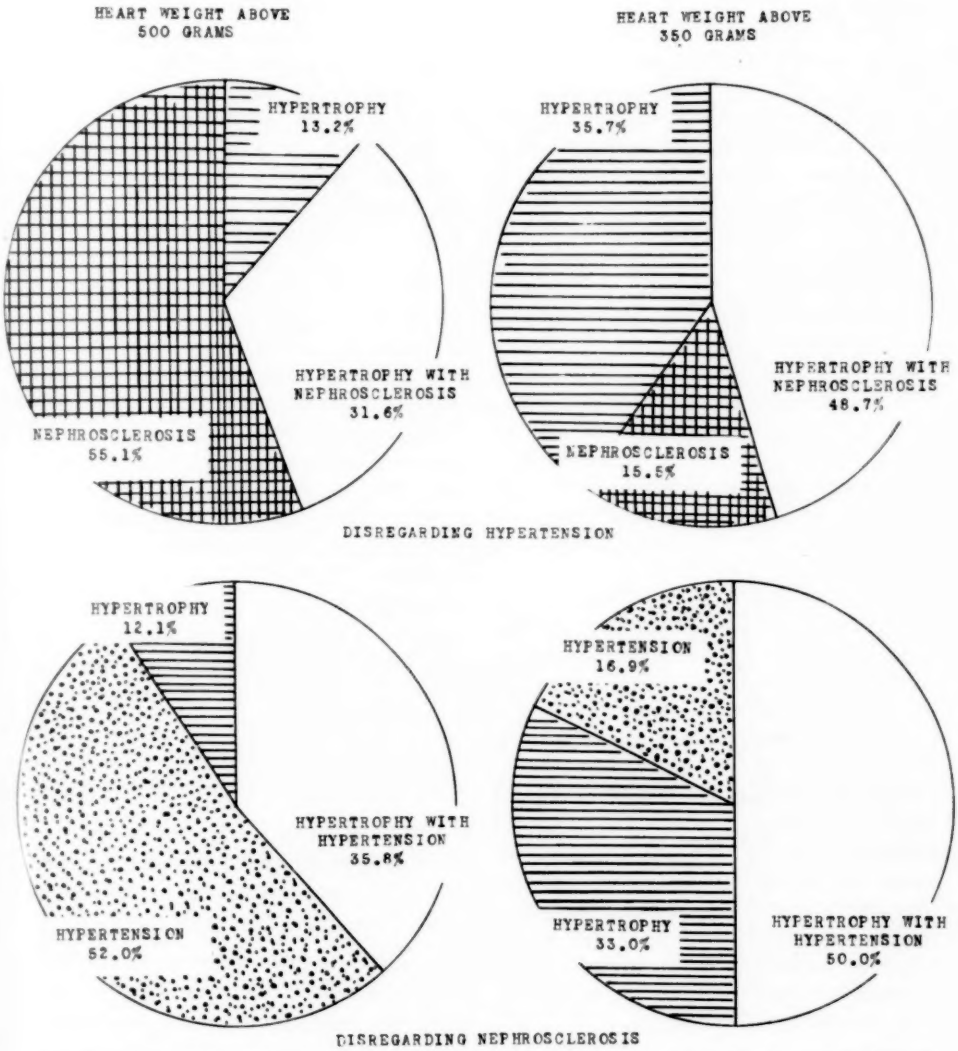

FIG. 1. Coincidence of hypertension, nephrosclerosis, and cardiac hypertrophy when either hypertension or nephrosclerosis is excluded from consideration.

pertension and 36% had nephrosclerosis without hypertension.

In an attempt to correlate the findings with age and sex, it was found that at the time of death in all groups the males were on the average 5 years older than the females. Negroes, representing one-third of the material, were 3 to 10 years younger than the whites.

Cardiac failure was the cause of death in 65% of the patients who had cardiac hypertrophy and nephrosclerosis without hypertension. In the group which had hypertension alone, 42% died as a result of a cerebro-vascular accident, 50% died of other causes, and 7% died in cardiac failure. No specific relationship was found in the cases which had cardiac hypertrophy or nephrosclerosis alone.

Discussion. The main observation of this study is the relatively small number of cases in the autopsy records in which cardiac hypertrophy, arteriolar nephrosclerosis, and hypertension coincided. If the diagnosis of cardiac hypertrophy is based on the stricter criteria adopted, the coincidence of these 3 factors occurs only in slightly more than one-fifth of the cases, and rises to almost one-third if a heart weight of over 350 gm. is taken to indicate hypertrophy. Possibly a similar lack of coincidence is not necessarily true to the same degree during life, since some of the blood pressure values obtained on admission of the patient to the hospital, occasionally shortly before his death, may have been lowered secondary to cardiac failure. It is recognized, however, that this factor explains only a limited number of cases. In the group in which cardiac hypertrophy and nephrosclerosis were found, without elevation of the blood pressure above 150/90, death from congestive heart failure was observed in two-thirds of the cases.

Consideration of the 2 levels of heart weight appeared justified by the results obtained. It permits the conclusion that the real incidence of cardiac hypertrophy lies between the 2 groups defined by the criteria used depending on other factors such as the total weight of the patient which was not available for consideration in this study. However, it should be pointed out that whatever borderline is applied, increased weight of the heart in the absence of either nephrosclerosis or recorded hypertension was found in a significant number of cases, 5% in Group A, and 18% in Group B.

Summary. In the autopsy material studied consisting of over 4168 cases in which at least 1 of the 3 factors, cardiac hypertrophy, arteriolar nephrosclerosis and hypertension (before death) was recorded, coincidence of all 3 was found in 21.7% of the cases with heart weight above 500 gm., and in 32.6% of the cases with a heart weight greater than 350 gm. Only part of this relatively low incidence of simultaneous occurrence of these 3 factors can be explained by a terminal drop in the blood pressure secondary to cardiac failure or peripheral vascular collapse. The numerical degree of the coincidence of the various factors is recorded. It is especially pointed out that cardiac hypertrophy may be found at autopsy in the absence of hypertension, nephrosclerosis, valvular, myocarditic or pulmonary lesions and congenital anomalies.

Conclusions. 1. The coexistence of cardiac hypertrophy, hypertension and arteriolar nephrosclerosis is the exception rather than the rule.

2. That cardiac hypertrophy occurs in the absence of hypertension and arteriolar nephrosclerosis is confirmed.

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THROMBOCYTOPENIC PURPURA: THE PROGNOSTIC AND THERAPEUTIC VALUE OF THE EOSINOPHIL INDEX, AN ANALYSIS OF 100 CASES*

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The pathogenesis of "primary" thrombocytopenic purpura is almost as obscure today as when the disease was first recognized as an entity. Since Kaznelson's recognition[4] of the part played by the spleen, splenectomy has become established as the treatment of choice. With the definition of the "secondary" thrombocytopenias (those due either to replacement or destruction of the marrow) there evolved a more precise limitation of, and indication for, splenectomy. The ready access to marrow *in vivo* has made the differentiation of primary and secondary thrombocytopenias much easier, but has been little utilized to further subdivide the "primary" types for either diagnostic or prognostic purposes.

In a previous report[8] it was suggested that a significant correlation existed between the number of eosinophils in the marrow and the clinical course of the patient. In the 30 cases reported it was shown that large numbers of eosinophils were indicative of a favorable prognosis and probably a spontaneous recovery, whereas normal or decreased numbers of eosinophils implied an unfavorable course and the necessity for splenectomy. Because of these findings it was thought that primary thrombocytopenias could be further subdivided into medical and surgical types. For the sake of brevity we have come to use the term Eosinophil Index in speaking of the relative numbers of eosinophils found in the marrow.

Seventy additional cases of primary thrombocytopenic purpura have been studied since the previous publication. The impressions gained from the original 30 cases had, therefore, ample opportunity for confirmation or denial. Some of the views previously expressed have had to be modified, but the principles laid down have not been altered. Both series were combined for the present study enabling us to analyze 100 cases.

Material and Methods. The present series consists of 100 cases of thrombocytopenic purpura. Marked platelet reduction, delayed clot retraction, prolonged bleeding time, petechiae, ecchymoses, and increased capillary fragility characterized all cases. The age extremes were 20 months and 90 years (Table 1). The duration of symptoms varied from 1 day to 20 years (Table 2). The racial and sex distribution is shown in Table 3.

Marrow preparations were made by direct smearing and were stained with May-Grunwald-Giemsa stains in every case.

The Eosinophil Index is determined by relating the number of eosinophils to the number of neutrophils at the metamyelocyte stage or later. This method obviates the necessity of correcting for lymphocytosis (in children) or erythroid proliferation (secondary to bleeding). Further advantage is that cells derived from the same root are being compared at

* Aided by a grant from the Wilson Laboratories, Chicago, Illinois.

stage when specific granulation makes differentiation definite. In the normal marrow the Eosinophil Index, *i.e.*, the number of eosinophils (at the metamyelocyte stage or later) per 1000 granulocytes (metamyelocytes or older) is less than 50. In the first series of cases the borderline between a high and low Eosinophil Index was approximately at this same level. For these reasons we have come to use 50 as the dividing point. An Eosinophil Index of more than 50 is said to be "high" and less than 50 "low." The Eosinophil Index was determined independently by 2 persons, each counting at least 1000 granulocytes.

Analysis of Cases. On the basis of the Eosinophil Index the cases were divided into high and low subgroups. These were further subdivided according to their course (Table 4).

TABLE 1.—DISTRIBUTION OF CASES WITH LOW AND HIGH EOSINOPHIL INDICES DIVIDED INTO AGE GROUPS. OF INTEREST IS THE MUCH GREATER INCIDENCE OF A "HIGH" EOSINOPHIL INDEX IN THE FIRST DECADE

Age in years		*0–5*	*6–10*	*11–20*	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*	*81–90*
Eosinophil Index	High	10	6	15	16	3	8	5	2		
	Low	1	1	8	5	13	2	2	1	1	1

TABLE 2.—DURATION OF SYMPTOMS. NO DEMONSTRABLE DIFFERENCE IN THE 2 TYPES OF PURPURA

Duration of Symptoms		*1–6 days*	*1–2 weeks*	*2–4 weeks*	*1–3 months*	*3–6 months*	*6–12 months*	*1–4 years*	*4–10 years*	*10–20 years*
Eosinophil Index	High	10	13	13	11	4	3	7	2	2
	Low	6	6	5	3	4	2	4	3	2

TABLE 3.—RELATIVE INCIDENCE OF THROMBOCYTOPENIA IN THE SEXES AND RACES, SHOWING NO SIGNIFICANT RELATIONSHIP TO THE EOSINOPHIL INDEX

		Male	*Female*	*White*	*Negro*
Eosinophil Index	High	24	41	53	12
	Low	11	24	26	9

TABLE 4.—FINAL OUTCOME OF THE CASES. MOST STRIKING DIFFERENCES ARE TO BE FOUND BY COMPARING SPONTANEOUS RECOVERY AND DEATH RATES IN THE HIGH AND LOW GROUPS

				Splenectomy					
		Number of cases	*Spontaneous Recovery*	*Successful*	*Unimproved*	*Died*	*Non-splenectomy Deaths*	*Chronic Purpura*	*Disappeared*
Eosinophil Index	High	65	29	25	1	0	6	1	3
	Low	35	8	8	2	8	7	1	1

A. *Spontaneous recovery.* This group encompasses those 37 cases which had a lasting rise of platelets to normal levels, with disappearance of clinical symptoms, due to, coincidental with, or in spite of conservative management. Of these 37 cases, 29 had high and 8 low eosinophil indices and represented 45% of the former against 23% of the latter group.

B. *Splenectomy.* Splenectomy was performed in 44 cases, 26 times in the high Eosinophil Index group and 18 times in the low. In the former, 96% resulted in permanent cure and only 1 case was unimproved. (It should be noted that this case was on the borderline, the index on 2 occasions being 50 and 51.) *There were no deaths in this group of splenectomized cases.* In the low index group only 44% of the patients splenectomized were cured and an additional 12% survived, but were unimproved. *Forty-four percent died in spite of splenectomy.*

C. *Non-splenectomy deaths*: There were 13 deaths before surgical intervention could justifiably be attempted. Six of these occurred in the high index group (9%) and 7 in the low group (20%). The cause of death in each instance was intracranial bleeding.

D. *Chronic Purpuras:* One case of chronic purpura was encountered in each category. Both refused splenectomy and remained unchanged while under conservative therapy.

E. *Disappeared from observation:* Four cases were followed for insufficient lengths of time to merit classification.

Discussion. The purpose of precise diagnosis is the achievement of accurate prognosis and correct therapy. In "primary" thrombocytopenic purpura splenectomy has become the treatment of choice. Even with splenectomy, however, the mortality rate still varies between 8 and 30%. Why, in a condition in which spontaneous recoveries are not uncommon, where some patients experience chronic, relatively benign courses for long periods of time, and where splenectomy is supposedly curative, the mortality rate should be so high, has been a question which has intrigued hematologists and surgeons alike.

During the past 10 years we have been dividing primary thrombocytopenic purpuras, according to the Eosinophil Index. This method of division has revealed that there exists 1 group of patients (high index) for whom the spontaneous recovery rate is approximately 50%. Should splenectomy be performed in this group, either because of extensive bleeding or too protracted a course, almost all of the patients will be cured. In sharp contrast is a second group of patients (low index) whose course is characterized by a low spontaneous recovery rate and a formidable mortality, even with immediate splenectomy. Because these group characteristics have remained constant and reliable in a large series of cases over a considerable length of time, we maintain that the term "primary" thrombocytopenic purpura is not sufficiently definitive and must be sub-classified in the search for more correct therapy and more accurate prognosis.

On the basis of early experience, we thought that a high Eosinophil Index represented a hypersensitivity state secondary to some offending agent or agents whose removal would break the pathogenetic mechanism. That this can occur is illustrated in Fig. 1. In most patients, however, the etiologic agent was not discovered even though the clinical course and the marrow were identical with those of patients whose etiologic mechanisms were uncovered. The eosinophilia remained as the sole common denominator.

In patients with a high Eosinophil Index return of platelets to normal

levels was usually noted in periods ranging from a few days to a few weeks. In several cases, however, no improvement was seen in several months. Splenectomy is the treatment of choice in these patients despite the fact that hypersensitivity may be suspected as causing the thrombocytopenia. The observation period and the decision as to the type of therapy must be further modified in the presence of severe bleeding or "malignant" purpura.* It is significant that we have never observed a relapse once spontaneous recovery occurred. Why these patients do not relapse remains an incompletely answered question. Whatever the precise mechanism may be, in the high index group it seems to be mediated through the spleen, as suggested by the uniformly beneficial effect of splenectomy.

Patients having primary thrombocytopenic purpura accompanied by a low Eosinophil Index seem to differ fundamentally from those in the preceding group. The lower incidence of spontaneous recovery, the high incidence of malignant purpura, the high mortality rate, and the frequent failure of splenectomy seem to support this thesis.

It is interesting to note that pediatricians fear primary thrombocytopenic purpura much less than do those accustomed to seeing the disease in adults. Of 29 children (less than 16 years of age) in this series, 23 (79%) fell into the high index group, and only 6 (21%) into the low. Furthermore, (Tables 5 and 6) marrow eosinophilia, spontaneous recovery and surgical cure occur

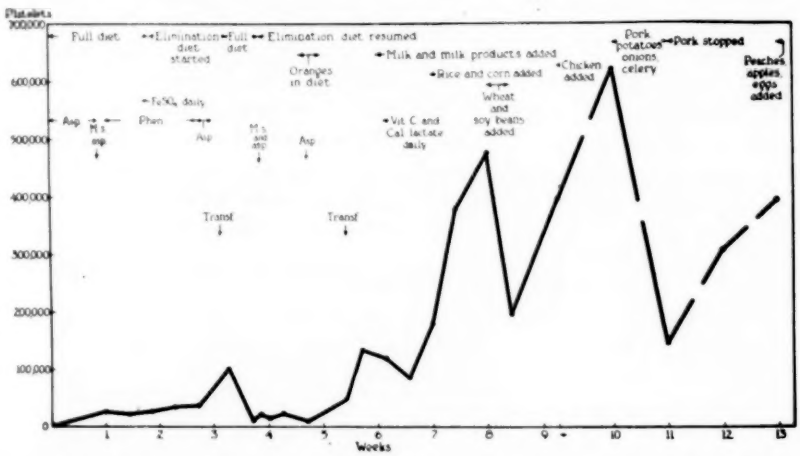

FIG. I. Platelet values in a case of thrombocytopenic purpura with a "high" Eosinophil Index. The influence of the addition and withdrawal of various foods on the platelet level is strikingly illustrated by this patient.

TABLE 5.—HIGH EOSINOPHIL INDEX IS MUCH MORE PREVALENT IN EARLY LIFE, THOUGH NOT LIMITED TO IT. NO SUCH PREVALENCE IS SEEN IN THE GROUP EXHIBITING A LOW EOSINOPHIL INDEX

		Under age of 30	*Over age of 30*
Eosinophil Index	High	47	18
	Low	15	20

* Characterized by fulminating onset, extensive mucous membrane bleeding, and large deep spontaneous subcutaneous hemorrhages.

more frequently in children and young adults than in the later decades. These findings agree with Elliott's observations on the relation of age to prognosis[2]. His figures were based on 87 cases of miscellaneous thrombocytopenic purpuras and did not include references to marrow eosinophils.

Of prime practical importance is the fact that the marrow eosinophilia is not mirrored in the peripheral blood. In only one instance was there a significant peripheral eosinophilia (13%). The reason for this is not yet apparent.

Demonstrable splenomegaly was the exception rather than the rule in our series, the spleen being palpable in only 12 cases. This figure contrasts strikingly with the statements in some textbooks indicating that one-third of the patients with primary thrombocytopenic purpura may be found to have demonstrable splenomegaly[9]. In our experience, the finding of a large spleen suggests a disease other than primary thrombocytopenia. Hertzog[3] found the average weight of 20 spleens from patients with primary thrombocytopenic purpura (patients over 20 years of age) to be 232 gm., while Pemberton[6], in a series of 57 cases found the average weight to be 201 gm.

Recently Diggs and Hewlett[1] reviewed 36 cases of thrombocytopenic purpura with special reference to the marrow findings. In their article they state that: "No correlation was found between the eosinophil counts and the deaths, recurrences or cures with or without splenectomy." However, the series are not comparable, as these authors eliminated from the analysis all those patients with a history of allergy or the taking of drugs. Notwithstanding this, they state: "we do not accept the thesis that eosinophil increase in the bone marrow is always indicative of sensitivity to exogenous food, drugs or other factors." It is conceivable that other agents, too, may produce marrow eosinophilia, factors completely unrelated to the presenting thrombocytopenia and, therefore, we agree that there is not *always* a cause and effect relationship. The problem of deciding whether a particular patient's thrombocytopenia has a hypersensitivity basis may be difficult. Madison's experience[5] substantiates our observations that thrombocytopenia on an allergic basis is not unusual. He states: "with advances in the technique of allergic studies, . . . it is likely that more cases will fall into the allergic category and to respond favorably to that method of therapeutic approach." Pohle and Cohen[7] have added further proof by specifically demonstrating a fall in the platelet level in allergic individuals following the ingestion of test foods.

Finally, reference must be made to the group of cases with a low Eosinophil Index in which there was spontaneous recovery. These emphasize the comment made in the previous publication[8] "that the findings here reported do not represent either

TABLE 6.—ULTIMATE RESULTS IN RELATION TO AGE GROUPS, SHOWING A BETTER PROGNOSIS FOR THE YOUNGER PATIENT

	Spontaneous Recovery	*Cured by Splenectomy*	*Deaths*	*Unimproved*	*Chronic*	*Disappeared*
Under age of 30	25	23	6	2	1	3
Over age of 30	12	10	15	1	1	1

fool-proof numerical prognostic system or a ready substitute for sound clinical judgment. Nonetheless, certain definite correlations are apparent, correlations which should add another tool to help make prognosis more certain and treatment more rational."

Summary. 1. One hundred cases of "primary" thrombocytopenic purpura are analyzed in an attempt to correlate the Eosinophil Index with prognosis.

2. On the basis of the Eosinophil Index, "primary" thrombocytopenic purpura is divisible into 2 groups: *a*, Those with a "high" Eosinophil Index (*i.e.*, increased numbers of marrow eosinophils), and *b*, Those with a "low" Eosinophil Index (*i.e.*, no increase in marrow eosinophils).

3. Significant prognostic differences are noted between the 2 groups.

4. Of 65 patients with a high Eosinophil Index, 54 (83%) were cured (45% spontaneously), and, more significant prognostically, none of the splenectomized patients died; whereas of 35 patients with a low Eosinophil Index, 16 (46%) were cured (23% spontaneously) and, most significant prognostically, 8 (44%) of the splenectomized patients died of their disease despite surgery. The total deaths in this series was 9% of the patients with a high Eosinophil Index and 43% of the patients with a low index, for an over-all mortality of 21%.

Conclusions. 1. With a high Eosinophil Index there is a marked tendency for spontaneous recovery, practically certain cure by splenectomy, and insignificant operative mortality.

2. With a low Eosinophil Index, there is but slight tendency for spontaneous recovery, splenectomy is therapeutically unreliable, and both the operative and over-all mortality are high.

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BLOOD "SLUDGE" PHENOMENON IN HUMAN SUBJECTS

Notes on Its Significance and on the Effects of Vasomotor Drugs*†

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Knisely[1,2] has described as "blood sludge", intravascular precipitation and agglutination of red blood cells in fatal malaria and other ominous pathological conditions. The inference has been made that such intravascular clumping of red cells occurs as a part of a morbid mechanism, that its presence indicates disease and that it occurs as a prelude to tissue damage. It is the purpose of this communication to explore the validity of this inference by observations on a variety of human subjects.

Method. Repeated day to day observations were made on a group of 35 patients with assorted diseases, including carcinoma, acute myocardial infarction, hypertension, pneumonia, pulmonary embolism and acute rheumatic fever. Also 5 apparently normal healthy subjects were examined for sludging daily for 10 months. All 5 (3 males and 2 females) were active members of the hospital staff and were free of significant body complaints or known systemic illness. The arterial blood pressure was determined by a sphygmomanometer cuff at the time of observation and records were kept of the occurrence of head colds, and minor bodily symptoms among these subjects and later correlated with the observations on sludging. Also a diary of events in the day to day life situation was recorded with data on prevailing mood, attitudes, emotions and feeling states.

A standard American binocular dissecting microscope similar to that illustrated in Knisely's report was used to make direct observations of the blood flow in the scleral and conjunctival vessels of these human subjects. A clear view was thus obtained at x30 magnification against the white scleral background. Empty vessel walls and white cells could not be identified at this magnification. The capillaries, venules and arterioles were visible only if they contained blood.

Results. Under circumstances of "normal flow" the vessels appeared to be of homogeneous red color. Single red cells were not distinguishable. Even in capillaries no particulate matter was seen. The various stages of blood sludging were identified as: 1, Streaming, *i.e.*, appearance of rapidly and evenly flowing particulate matter and granules along the course of the vessel in which clumps or individual red cells were not distinguishable; 2, Sludging, *i.e.*, distinguishable clumps of red cells of varying size which flowed slowly, intermittently or not at all. These red cell aggregates were separated by varying amounts of clear plasma.

* Aided by grants from the Commonwealth Fund and the Estate of Lester N. Hofheimer.

† This and the following article, which reached us on the same day, are so mutually confirmatory that together they seem to us to present compelling views on the subject. See also Am. J. Med. Sci., **219**, 249, 1950, for a recent article by Knisely. [Ed.]

Among the group of patients with various diseases there was observed in the same individuals wide daily fluctuations in the presence and degree of sludging. No consistent correlation was established between sludging and the clinical state of the individual as regards symptoms, fever, blood counts or changes in sedimentation rate of the red cells. In some, sludging was never seen while in others sludging was typical only in the convalescent stage of their illness. When sludging was observed it was frequently not widespread. It was seen to occur occasionally in only 1 or 2 vessels, or occasionally in as many as 90% of the vessels accessible to view. There was very much variation in the same subject from day to day. Typical observations are illustrated in Table 1.

In the long term observations in normal subjects, great variation in sludging was also recognized. Marked and generalized sludging was repeatedly observed in 4 of the 5 subjects. In the fifth only localized sludge in a small fraction of the vessels was ever noted. These subjects displayed the same degree and variability of the sludging phenomenon as was seen in the group of patients. Often no sludging was seen in any of the vessels. As among the patients, it was repeatedly observed that large particles and marked stasis of flow occurred in a few vessels while the remainder of the vascular bed appeared normal.

The red cell aggregates were not consistently associated with furuncles, nasopharyngitis, fever, fluctuations in blood pressure, with variations in life situations and emotional state of the subjects, or with menses.

Stasis at the bifurcations of vessels was often observed, but no vessel spasm or constriction was visible at these points. The column of clumps separated by plasma often halted and then moved on again as a clump moved into a larger stream. In 2 of the healthy subjects, segments of vessels containing packed and stationary clumps were repeatedly observed to remain for as long as 3 days. Thereafter, the "pseudothrombus" disappeared, leaving no visible trace.

Local Vasodilatation and Sludge. The only consistent association observed was that between the degree of sludge and the degree of local vasodilatation in the conjunctiva. At times when many vessels of all sizes were widely visible in the same person, there was more hesitant slow flow of the clumps than when the width and number of vessels was reduced. This finding suggested an alternate interpretation that sludging was a phenomenon of reduced velocity of the stream or of reduced centrifugal force from increased volume of the capillary bed. Thus the occurrence of sludging would appear to be due to the slowing of blood flow rather than the cause of the slowing.

In order to explore further this possibility 8 patients with marked generalized sludging were given 2 drops of a 10% ophthalmic neo-synephrine solution in one eye. Continuous observations were then made during the ensuing rapid vasoconstriction. Arterioles and venules promptly narrowed and many capillaries disappeared entirely within 20 to 30 minutes. With vasoconstriction the clumps of sludging disappeared in the eyes of 6 subjects and in the other 2 it was greatly diminished so that only fine particles could be seen in the larger vessels. Spurting fluid columns were evident in arterioles. In all 8 the opposite untreated control eye showed no change in the amount or degree of sludge.

Five subjects without visible sludging were given flushing subcutaneous doses of 1.0 mg. of histamine phosphate. Within 10 minutes there was

TABLE 1.—TYPICAL DAILY OBSERVATIONS ON 10 PATIENTS INDICATING THE LACK OF CONSISTENT CORRELATION BETWEEN SLUDGING AND THE SEDIMENTATION RATE OR TEMPERATURE

		Observation 1				*Observation 2*				*Observation 3*				*Observation 4*			
		Sludge		*Sed.*		*Sludge*		*Sed.*		*Sludge*		*Sed.*		*Sludge*		*Sed.*	
Patient	*Diagnosis*	*%*	*Degree*	*Rate*	*Temp.*	*%*	*Degree*	*Rate*	*Temp.*	*%*	*Degree*	*Rate*	*Temp.*	*%*	*Degree*	*Rate*	*Temp.*
1	Myocard. infarct.	0	0	35	38.5	10	++	56	37.5	80	++	25	37	50	+++	16	37.8
2	Myocard. infarct.	20	+++	20	39.0	0	0	42	38.2	100	++	60	37.2	80	+	27	37.4
3	Myocard. infarct.	50	+	38	38.6	100	+++	27	37.4	100	+	40	37.5	20	++++	12	37.7
4	Malig. hypertension	5	++++	8	37.4	90	++	15	37.4	50	+	—	37.2	20	+++	10	37.8
5	Ac.Rheum. fever	20	+	54	38.6	0	0	40	38.0	40	+++	22	37.1	0	0	25	37.5
6	Ac.Rheum. fever	100	++	33	38.0	80	+	28	37.8	0	0	57	37.8	25	++++	9	37.4
7	Mult.myeloma	100	+++	—	37.1	0	0	24	37.5	10	+	—	37.2	80	+	56	—
8	Leukemia (Myel.)	5	++++	—	—	20	++	32	37.4	5	++++	82	38.5	100	+++	78	39.9
9	Broncho pneum.	0	0	35	39.4	0	0	49	38.0	100	++	24	37.5	50	+++	14	37.7
10	Lobar pneum.	60	+++	—	40.1	10	+	53	37.4	100	+	—	37.4	10	++++	—	37.2

%—Approximate percentage of conjunctival vessels involved
Sed. Rate: in mm. Rr.
Temp.: °C.
Degree: Ranges 0 to ++++:
+: Streaming of fine particles
++: Large particles flowing rapidly and evenly
+++: Large particles flowing slowly and hesitantly
++++: Stasis and pseudo-thrombus formation

evident vasodilatation of the conjunctivae with associated widespread sludging. These changes observed following either local neo-synephrine or histamine subsided within 1 or 2 hours.

Conclusion. On the basis of day to day studies of normal subjects and patients with a variety of disease states and of observations with vasomotor drugs, it is suggested that blood sludging in the conjunctivae is the result of an increase in the volume of the local vascular beds and a decrease in the velocity of blood flow. Moreover, it is evident that widespread sludging in the conjunctival vessels is compatible with good health and well being.

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+ : Large particles flowing rapidly and evenly
++ : Large particles flowing slowly and hesitantly
+++ : Stasis and pseudo-thrombus formation

A CLINCAL EVALUATION OF THE BLOOD "SLUDGE" PHENOMENON

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The phenomenon of blood "sludging" has received considerable attention during the last 6 years, Knisely[4,10] and his associates especially having emphasized through their exhibits, motion picture demonstrations and publications in the lay and scientific press, the role which they believe the phenomenon plays in physiology and pathology. It is our purpose to demonstrate that blood sludging is essentially a reversible intravascular agglutination or clumping phenomenon caused by the same factors which are responsible for a rapid blood sedimentation rate, namely the increased rouleaux forming tendency which develops in blood when there are certain changes in plasma proteins and other blood constituents.

Intravascular sludging has been described in the past under other names. The excellent reviews of Fahraeus[1,2] and the more recent review by Knisely and associates[9] emphasize the wealth of knowledge regarding the phenomenon which has accumulated during the preceding centuries. The phenomenon commonly occurs in man and other mammals and reflects in a general way the state of health of the individual whose blood is being investigated.

During our studies of the blood sedimentation phenomenon it was noted that intravascular agglutination as described by Fahraeus did occur in patients with a rapid sedimentation rate. During the past year we have made over 1200 observations of the conjunctival capillary circulation and have in general found a close correlation between the blood sedimentation rate and the degree of sludging in the capillaries.

Methods. A standard Leitz capillary microscope with 15 watt tungsten illumination was used for all the observations. The patient is examined in the reclining position and the microscope is placed upon the patient's face so that the objective is directly over one eye. The patient is then directed to look to either side in order to bring the sclera into view. The conjunctival capillaries are then brought into focus. Patients are usually able to cooperate well during the examination. Occasionally it is necessary for the examiner to hold the eye lids apart with his free hand. After a short period of training it is possible for the examiner to observe the circulation in a group of capillaries for as long as 15 seconds. The magnification is not great enough to see individual cells clearly but it is possible, however, to observe the degree of aggregation of the erythrocytes and the velocity of the circulation. An arbitrary standard of + to ++++ was established to evaluate the degree of sludging in the capillaries. This type of subjective qualitative evaluation is quite crude, nevertheless it can be significantly informative when practiced by a single observer or a team of observers. Unfortunately it is difficult to compare such data with the observations of others with any degree of quantitative accuracy. We know of no other way of recording or evaluating a complex dynamic phenomenon of the circulation such as this. After making over 500 preliminary

examinations we were able to recognize the maximum amount of sludging in the capillaries. This appeared as very coarse granular accumulations of erythrocytes separated from each other by spaces containing clear plasma. The whole column of blood moved slowly and at times haltingly. This was designated as ++++ sludging.

Sedimentation rates were determined by the Westergren method.

Serum proteins were determined by the method of Cohn and Wolfson.

Results. There was a close correlation between the sedimentation rate and the degree of sludging in 82.4% of the 619 cases studied. There was a very wide distribution of all types of disorders in this group of patients. All the diseases ordinarily seen in a large general hospital were represented. All age groups except infants and small children were investigated.

The cases were separated into 4 groups of sedimentation rates in order to compare them with the 4 groups representing the degree of sludge formation. Table 1 shows the correlation between the sedimentation rate groups and the degree of sludging.

The group in which there was no correlation between the sedimentation rate and the degree of sludging (17.6%) was given further study. This group was separated into 2 groups, cases in which the sludging was less than the sedimentation rate (5.5%) and those in which it was greater (12.1%) (Table 2).

Rapid blood sedimentation, well developed sludging and hyperglobulinemia were frequently associated together. Such a concurrence was to be expected because of the strong rouleaux forming properties of the serum globulins.

Sludging and rapid sedimentation were frequent in anemic individuals. On the other hand, no sludging and an absence of sedimentation was observed in each of 5 cases of erythrocytosis (polycythemia vera and congenital heart disease).

TABLE 1.—1000 OBSERVATIONS (619 CASES) OF BLOOD SEDIMENTATION RATES CORRELATED WITH THE INTENSITY OF BLOOD SLUDGE FORMATION

Degree of Sludging	*Sedimentation Rates*							
	0–20 mm.		*20–60 mm.*		*60–100 mm.*		*Over 100 mm.*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
0+	123	76.4	36	9.5	7	2.3	0	0
++	18	11.2	249	65.5	22	7.2	15	9.7
+++	19	11.8	63	16.6	249	81.9	38	24.5
++++	1	0.6	32	8.4	26	8.6	102	65.8
Totals	161	100	380	100	304	100	155	100

Discussion. Our observations indicate that the blood sedimentation phenomenon is merely the *in vitro* manifestation of the process of sludging *in vivo*. In this we are in complete agreement with the observations of Fahraeus[2]. It has been known for many years that the phenomenon of erythrocyte sedimentation is a manifestation of Stoke's Law and that increased rouleaux aggregation among the erythrocytes is the immediate cause of the increased rate. Rouleaux aggregation itself is a product of properties of the erythrocyte surface and plasma proteins, particularly fibrinogen and other globulins[3]. Fahraeus[1,2] and

TABLE 2.—SLUDGING AND SEDIMENTATION RATES IN VARIOUS DISEASES

Group 1. Sludging Less Than Sedimentation Rate

Pneumonia		10
Heart Disease		7
Rheumatic Fever Acute	1	
Pericarditis	1	
Arteriosclerotic Heart Disease	3	
Hypertension	2	
Kidney Disease		5
Nephritis	3	
Pyelocystitis	2	
Carcinomatosis		3
Acute Alcoholism		4
Miscellaneous		5
Gonorrheal Arthritis	1	
Asthma	1	
Anemia, Refractory	1	
Cellulitis	1	
Arthritis Acute	1	
		34

Group 2. Sludging Greater Than Sedimentation Rate

Dermatitis		5
Heart Disease		40
Acute Myocardial Infarction	7	
Syphilitic	5	
Arteriosclerotic	16	
Hypertensive	4	
Rheumatic	3	
Endocarditis	2	
Coronary Insufficiency	3	
Cerebral Hemorrhage		5
Hepatic Cirrhosis		10
Pulmonary Disease		5
Bronchogenic Carcinoma	2	
Tuberculosis	2	
Bronchiectasis	1	
Rheumatoid Arthritis		2
Nervous Disease		3
Neuritis, Peripheral	2	
Paralysis Agitans	1	
Miscellaneous		5
Arteriosclerotic Gangrene of Foot	1	
Carcinoma of Liver	1	
Carcinomatosis	1	
Leukemia	1	
Esophageal Stricture	1	
		75

others[12,13,14] have demonstrated that the phenomenon occurs *in vivo* and, when present, results in changes in the stream of circulating blood. Knisely during the last decade observed this phenomenon in malaria and other pathologic conditions[4-6,8]. He apparently was not, until recently, familiar with the work of Fahraeus. Because of this, confusion has developed and many clinicians believe that blood sludge is a newly discovered entity of considerable pathologic importance. Knisely[6], a few years ago, insisted that blood sludging differs from intravascular rouleaux aggregation. This may be true in cases of *Plasmodium knowlesi* malaria in monkeys, but many doubt if sludging is in any way different from the intravascular rouleaux aggregation of Fahraeus, at least as far as man and his pathology is concerned. Knisely[4,7,10] has stated that the sludging occurs when a sticky fibrin like deposit forms on the erythrocytes, causing them to adhere one to another. However, sludge formation is not prevented by heparinization[11]. This should indicate that fibrin does not have a part in the phenomenon.

The rapidity of the circulation of the capillaries depends upon cardiac efficiency and the peripheral resistance in the capillaries themselves. This resistance depends upon the viscosity of the blood and the caliber of the capillaries. Blood viscosity is almost directly proportional to the concentration of the erythrocytes. If clumping of erythrocytes occurs intravascularly and clumps of viscous erythrocyte mass enter the small capillaries, a slow and interrupted flow develops in those capillaries. Clumping increases because the movement of the circulation is slow. Fragile clumps which form in the larger vessels do not increase in size because of the rapidity of the blood stream. However, in the small capillaries, where there is a slow movement of blood and at times almost complete stasis, contiguous clumps readily adhere to each other and the sludge mass increases in size. Rouleaux aggregation is more intense in anemia because there is more plasma protein in each volume unit of blood to affect the erythrocyte surface. The opposite

conditions prevail in erythrocytosis. In heart failure the cardiac output is often reduced and the circulation time is increased. The motion of the circulation is less and sludge formation is protected. This may explain the discrepancy between the sedimentation rates and the degree of sludging in the 40 cases of heart disease which we observed.

Summary. 1. The bulbar conjunctival capillary circulation was observed in patients with a wide variety of diseases. A close correlation between the degree of blood "sludge" formation and the erythrocyte sedimentation rate was found in 82.4% of the 619 cases studied.

2. Blood "sludge" formation is a product of rouleaux aggregation and stasis within the capillaries.

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ELECTROCARDIOGRAPHIC PATTERNS IN HYPOPOTASSEMIA: OBSERVATIONS ON 79 PATIENTS*

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The subject of hypopotassemia has recently assumed considerable importance because of: 1, the recognition of the number of conditions in which alterations in the concentration of this electrolyte occur within the body; 2, the serious disturbances that occur in the body when the serum potassium is abnormally high or abnormally low; 3, the rather simple methods by which alterations in the serum potassium may be observed by the electrocardiogram; and 4, the complete reversibility of this process following the administration of potassium.

Considerable confusion exists regarding the electrocardiographic evidence of hypopotassemia because of the various patterns observed in different patients. Questions which we sought to answer in this study were as follows: 1, Is there a single characteristic electrocardiographic pattern in hypopotassemia? 2, If not, what patterns are observed? 3, What is the relative frequency of such patterns in various etiologic states associated with hypopotassemia? 4, Which of the 2 major changes is most characteristic of this electrolyte imbalance: alterations in the T wave and ST segment, or the prolongation of the QT interval? 5, What is the relationship, if any, between the degree of change and the serum potassium level? 6, What modification of the electrocardiographic pattern is caused by other electrolyte alterations associated with the low serum potassium?

The alterations in the electrocardiogram associated with a high serum potassium have been described in various conditions such as azotemia[14,16,18,19], Addison's disease, and diabetic acidosis[25]. These consist of an increased amplitude of the T wave with narrowing at the base between the 2 limbs of the T wave (Fig. 3 (Pre Rx tracing)). In addition, widening of the QRS complexes may also be present. These changes return to normal as the levels of the serum potassium approach normal.

Except for reports on isolated cases[9,13,17,22,25] there is relatively little in the literature relative to the electrocardiographic alterations associated with a low serum potassium. Recognition of the electrocardiographic patterns in hypopotassemia is of importance because of their help in the diagnosis of this state and in following the results of therapy. While electrocardiographic patterns are by no means a substitute for the chemical estimation of this electrolyte, when the latter is not avail-

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able they are of qualitative importance. Moreover, the easy availability of this method of study considerably enhances its usefulness.

Low concentrations of potassium in the serum and diminution in cellular potassium have been observed in the following conditions: 1, diminished intake of potassium; 2, animals and patients treated with large doses of desoxycorticosterone; 3, familial periodic paralysis; 4, diabetic acidosis; 5, Cushing's syndrome; 6, fluid loss in intestinal obstruction; and, 7, diarrhea.

The electrocardiographic changes similar to those to be described in this paper, were observed by Bellet and Dyer[1] (1937) following emergence from diabetic acidosis in 17 patients. At that time they were thought to be due to electrolyte changes but not specifically to potassium alterations. These tracings manifested lengthening of the QT interval, depression of the ST segment and inverted T waves. Recently these changes have been ascribed to a low serum potassium by Holler[17], Nicholson and Branning[25], Martin and Wertman[22], and this has been confirmed by studies in our laboratory in diabetic acidosis[23] and in various states accompanied by vomiting[4,5]. The initial observations of electrocardiographic changes in hypopotassemia were made in patients with familial periodic paralysis[30,31] (1940-41). In addition, Thompson[33] (1938) published records of a patient with Addison's disease where hypopotassemia resulted from the administration of desoxycorticosterone acetate. A similar case in which, however, serum potassium values were not furnished, was published by Currens and White[8]. Brown, Currens and Marchand[7] reported 2 patients with muscular paralysis in chronic nephritis which was attributed to potassium loss. Serum potassium values were not determined. Ellis[11] reported the electrocardiograms of 4 prisoners of war suffering from severe malnutrition and diarrhea. The electrocardiographic changes closely resembled those of hypopotassemia, although other factors were probably operative in their production. Treatment of these patients resulted in a return of the records to normal.

Material and Methods. This study is based on a study of serial tracings in 79 patients in whom hypopotassemia was the result of several different conditions which are shown in Table 1.

TABLE 1.—CAUSES OF HYPOPOTASSEMIA

	No. of Patients
Diabetic Acidosis	35
Vomiting due to Intestinal Obstruction	34
Miscellaneous Group	
Familial Periodic Paralysis	1
Inanition	2
Administration of Adreno-corticotrophic Hormone	1
Colitis	2
Prolonged Administration of Parenteral Fluids	2
Nephrosis with Diuresis	2
TOTAL	79

In all, 380 electrocardiograms correlated with serum potassium and other electrolyte estimations were recorded. On admission to the hospital, the blood carbon dioxide combining power, pH, protein, chloride, blood urea, nitrogen, calcium and potassium were estimated. Simultaneously, an electrocardiogram, including Leads I, II and III and Precordial Leads CR2, CR3, CR4 and CR5, was taken. These studies were repeated at frequent intervals, depending upon the individual case, until the electrocardiogram returned to normal. Thirty of these patients were given potassium intravenously in a dose of from 300 to 1500 cc. at a rate of 3 to 5 cc. per min. in a concentration of 1.14% (155 mEq./liter). This electrolyte was also administered by hypodermoclysis in 10 additional patients and by mouth in 10 patients.

The serum potassium estimations were made initially with a Perkin-Elmer and later with a Beckman flame photometer.

The Measurement of Electrical Systole (QT, QU Segment). The measurement of the QT interval length is not always a simple

matter because the end of the T wave is frequently not clearly demarcated. In this study Precordial Leads CR2, CR3 and CR4 were used for this measurement, as we[4,5] have found that these leads give the clearest and most marked evidence of hypopotassemia. That lead in which the termination of the T wave was most clearly seen, and where the QT interval was longest, was used for the measurement. Considerable differences were found between the T wave and ST segment changes in the limb and precordial leads.

Another complicating feature in the measurement of electrical systole was the presence of a more or less prominent U wave which followed the T wave at various intervals. It appeared in the form of a T wave notching, or following the T wave with an intervening depression which did not reach the iso-electric line (Figs. 4 and 5). It is doubtful whether electrical systole should be measured to the end of the T wave (QT interval) or to the end of the U wave (QU interval). That the U wave should be considered as part of electrical systole is an opinion held by many physiologists[12,24].

Findings. Hyperpotassemia was observed by us in 25 patients with diabetic acidosis prior to treatment and in 8 patients with azotemia. Their electrocardiographic findings are similar to those previously reported[14,16,18,19], *i.e.*, tall, narrow T waves often accompanied by some widening of the QRS complexes. These are reversible and give way to T waves of normal amplitude and configuration when a normal serum potassium is restored.

The remaining cases in the series showed for the most part a hypopotassemia when they first came under our observation. The diagnosis was based on: *a*, the presence of a cause—such as diabetic acidosis, vomiting; *b*, the complete reversibility of this pattern following the administration of potassium; and, *c*, chemical determination of the serum potassium. In patients with diabetic acidosis, we were able to follow the electrocardiographic pattern in the same patient from the stage of hyperpotassemia, to normal serum potassium and to hypopotassemia during the course of treatment in a period of 3 to 12 hours. Thereafter the electrocardiogram returned to normal when the serum potassium returned to normal, usually when the patient was able to take food by mouth.

Electrocardiographic Changes. There is no single electrocardiographic pattern which may be said to be pathognomonic of hypopotassemia. In all, 5 electrocardiographic patterns were observed, as shown in Table 2. However, 64 of the 79 patients (81%) showed Patterns 1 and 2; the remainder, 15 patients (19%), showed the Patterns 3, 4 and 5.

The alterations in the electrocardiogram as a result of hypopotassemia are confined chiefly to the T wave, ST segment and QT interval. A prominent U wave is of additional diagnostic import and will be discussed below. Other observed alterations of lesser diagnostic significance are elevation of the ST segment and arrhythmias, *e.g.*, ventricular and auricular premature beats and auricular fibrillation.

The following are the 5 characteristic patterns:

Pattern 1 (shown by 33 patients) consisted of a depression of the ST segment accompanied by lengthening of the QT interval. The degree of ST segment depression and lengthening of the QT interval varied in general with the degree of hypopotassemia (Figs. 1a and b). With increasing degrees of hypopotassemia the ST depression became more marked; in more severe grades the initial portion resembled an inverted T wave (Fig. 1b).

Pattern 2 (shown by 31 patients) consisted of T wave inversion accompanied by QT prolongation, frequently followed by a U wave. The T wave inversion was of 3 types: First, the inverted T wave manifested a slight elevation of the initial portion of the ST segment followed by terminal downward dip. This T wave pattern resembles quite closely that seen in

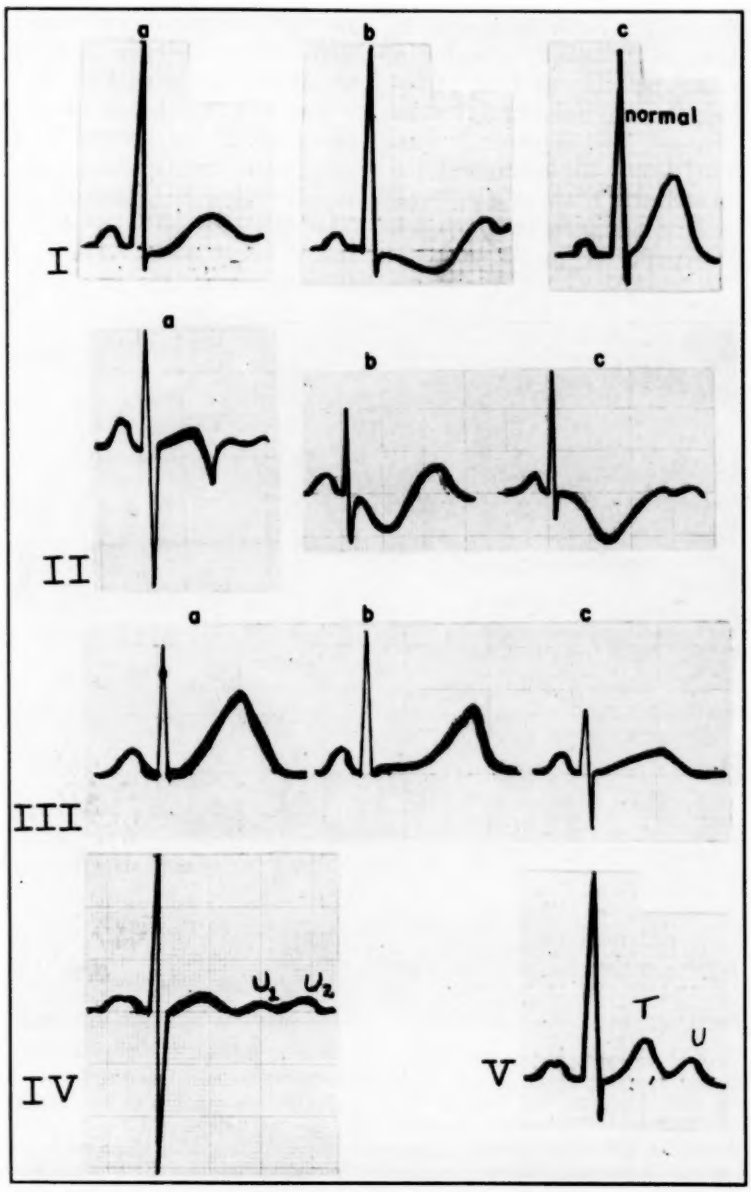

FIG. 1.—Semi-diagramatic representation of electrocardiographic changes of various patterns observed in hypopotassemia drawn to scale from actual tracings. (A) a and b represent different degrees of ST segment depression observed in Pattern 1. c—normal control. Note the slight ST segment depression in b, the more marked ST segment depression with QT prolongation in c. The initial portion of the T wave shows a slight tendency toward inversion. Pattern 2: a, b and c represent the different types of T wave inversion. See description in text. Pattern 3 shows different degrees and types of upright T waves accompanied by QT prolongation. In a and c the prolonged QT segment takes up practically all of the T wave. In b an isoelectric period is observed between the QRS and T wave. Pattern 4 shows a T wave of low amplitude which is almost isoelectric followed by 2 undulations which are probably U waves. Pattern 5 shows a T wave followed by a prominent U wave.

acute pericarditis with subepicardial myocarditis, in transient episodes of coronary insufficiency, and in certain states of myocardial infarction (T wave influx). Second, the inverted T wave was situated below the isoelectric line. Third, the inverted T waves manifested *little or no deviation from the isoelectric line* and, except for prolongation of the QT segment, resembled the inverted T waves seen in various types of myocardial disease.

PATTERN 3 (shown by 6 patients) consisted of an upright T wave, the amplitude of which was normal, slightly below, or slightly above normal. The QT interval was prolonged and the T wave occupied the entire QT

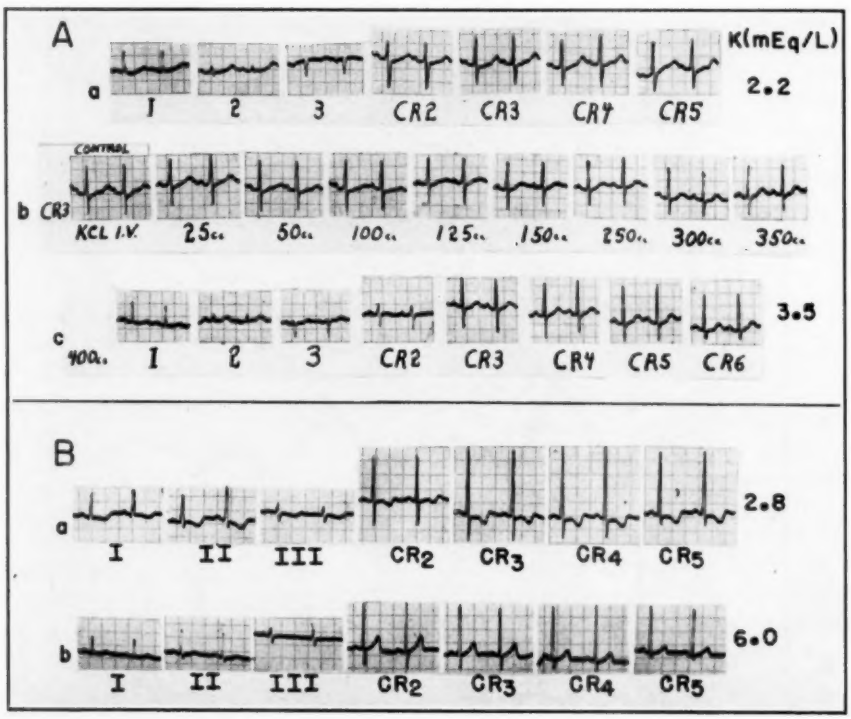

FIG. 2.—*(A)* E. L., female, white, age 75, was admitted to the hospital 5/15/49 with a history of diarrhea and vomiting for 3 days. a, Control electrocardiogram taken 5/20/49. Note long QT interval with depressed RT segment (Pattern 1). QT measures 0.44 sec. (theoretical QT for this rate, 0.31 sec.). The serum potassium level at this time was 2.2 mEq./liter. b, CR3, note shortening of QT interval with disappearance of ST segment depression and upright T waves which appeared following increasing doses of isotonic KCl administered intravenously. c, Leads 1, 2, 3, CR2, CR3, CR4, CR5 and CR6 after 400 cc. of potassium chloride in 2½ hours. The QT interval measures 0.32 sec. (theoretical QT, 0.32 sec.). The serum potassium level at this time was 3.5 mEq./L.

(B) A. L., female, white, age 49, was admitted to the hospital suffering from inanition due to gastric carcinoma. a, Control tracing shows inversion of T waves in all leads with slight prolongation of the QT segment. The QT measures 0.36 sec. (theoretical QT for this rate 0.327). The serum potassium level was 2.8 mEq./L. b, After administration of 1000 cc. isotonic potassium chloride intravenously in 6 hours. Note upright T waves in all leads and shortening of the QT interval which now measures 0.28 sec. The serum potassium level at this time was 6.0 mEq./L.

segment, extending from the beginning of S to the end of the T wave. There was usually no isoelectric period between the S wave and the initial ascent of the T. A few exceptions were observed where an isoelectric period was seen; this occurred in the presence of alkalinosis with and without hypocalcemia.

Pattern 4 (shown by 5 patients) consisted of a T wave, which was almost isoelectric, accompanied by a terminal U wave. The end of the QT was not clearly demarcated in this pattern, and it is probably best to refer to this as a QU wave. Following the administration of potassium, the U wave disappeared and the T wave returned to normal amplitude (Fig. 5b).

Pattern 5 was observed in 2 of our patients with vomiting due to intestinal obstruction. The T wave itself was normal in amplitude. The U wave was unduly prominent and followed the T wave after the downstroke had reached the isoelectric line. The QT interval proper was not prolonged; the prolongation involved the QU interval (Fig. 5) or the entire electrical systole.

It was of some interest to follow the evolution of the T wave changes accompanying hypopotassemia in the same patient. This could be best accomplished in diabetic acidosis where one could observe the entire gamut of change, from the T wave changes accompanying hyperpotassemia, through the changes of normal serum potassium, to those of hypopotassemia, in a few hours. We followed 3 such patients with electrocardiograms and serum potassium estimations every 15 minutes following the administration of insulin and fluids. It was observed that the T wave amplitude gradually decreased to a normal amplitude as the serum potassium dropped to normal. Then the T waves decreased slightly in amplitude. The transition to the inverted T wave observed in Fig. 2b was usually abrupt and occurred within 10 to 15 minutes.

U. Waves. Significant U waves were observed in 42 of the 79 patients (53%). They were observed in 13 of the diabetic group, 22 of the vomiting group and 7 of the miscellaneous group. It is of interest that in the vomiting group not only was the incidence of U waves highest, but also they were the most prominent. In the diabetics the U wave never attained the prominence observed in most vomiting patients; the U waves observed in the patients with fluid loss due to colitis, diarrhea and following use of parenteral fluids resembled those of the vomiting cases.

In quoting the above figures on the incidence of U waves it is recognized that some inaccuracies exist because of the short diastole accompanying high rates (in man the maximum rate at which a U wave is best observed is between 90 and 100), and because the U wave is the least clearly defined of all the ECG waves. They present many bizarre characteristics and positions, and may be part of notched T waves; they may be upright or inverted, single or multiple.

Relation between QT Segment Prolongation and Degree of Hypopotassemia. Correlation between the level of the serum potassium and the degree of QT segment prolongation (QT_c)[32] was made in 42 electrocardiograms from patients with diabetic acidosis and in 38 from patients with vomiting.

The statistical correlation between the length of the QT interval and the serum potassium concentration has been reported previously in a series of cases of diabetic acidosis[22,25] and was found to be highly significant ($r = -0.73$; $p = < .0001$)[22]. The same correlation studies were per-

formed on this present series of cases of diabetic acidosis and showed similar correlation. The statistical correlation between the QT interval corrected for rate (QT_c) and the serum potassium concentration in cases of fluid loss due to vomiting ($n = 38$) has also been found to be significant ($r = -.67$: $p = <<< .0001$).

In cases of diabetic acidosis, the mean QT_c corresponding to serum potassium values below 4.0 mEq./liter was found to be 0.504 secs. ($n = 30$). The mean QT_c corresponding to serum potassium concentrations above 4.0 mEq./liter was found to be 0.403 secs. ($n = 27$). Application of the "t test" to these means gave a t value of 2.93 with a p of .003. A similar calculation in cases of vomiting ($n = 43$) gave a t value of 4.33; $p = .00015$. Thus a significant difference exists between the mean QT interval corresponding to potassium concentrations below 4.0 mEq./liter and the mean QT interval corresponding to potassium concentrations above 4.0 mEq./liter.

Relation between the Electrocardiographic Pattern and Etiology of Hypopotassemia. The relative incidence of the T wave and ST segment pattern in diabetic acidosis and cases of vomiting due to intestinal obstruction is of some interest. In the cases of diabetic acidosis the common pattern observed was inversion of T waves of various types (Pattern 2). This was observed in 24 of the 35 cases (66%), whereas Pattern 1, or ST segment depression, was observed in 9 cases (26%). In the vomiting cases, however, Pattern 1, or ST segment depression, was observed in 18 of 34 cases (53%), where T wave inversions were observed in only 8 (27%). U waves were observed with less frequency and were only of slight or moderate prominence in the diabetics; they were observed more frequently and tended to assume their highest amplitude in vomiting cases and in those cases in which fluid loss resulted from colitis and diarrhea.

We do not know the reason for these differences. These changes apparently occur irrespective of age and preexisting heart damage. They may be related to the manner and rapidity of the production of hypopotassemia in these 2 groups of cases, the presence of acidosis in the former and alkalosis in some of the latter, and the effect of other electrolytes on these derivations.

Effect of Potassium Administration on the Electrocardiogram of Hypopotassemia. The 30 patients who received isotonic potassium chloride by vein were studied by serial electrocardiograms. In general, the rapidity with which the electrocardiogram returned to normal depended upon the speed and the amount of potassium administered, and the return to normal was accomplished by a simultaneous decrease in prominence of the U wave, shortening of the QT or QU segment, decrease in inversion of the T wave or decrease in depression of the ST segment, followed by a gradual increase in amplitude of the upright T wave with a return of the QT segment to normal. In almost all of our patients the electrocardiogram returned to normal as the serum potassium attained a normal range. The electrocardiograms, however, rather rapidly tended to revert to the hypopotassemic pattern following the cessation of potassium administration (Fig. 3). This is probably the result of a shift of potassium from the extracellular fluid into the cell, its elimination in the urine and its utilization in various physiological processes. In order to maintain a normal serum level potassium had to be continually supplied by parenteral injection unless the patient was able to take food by mouth.

When potassium was administered by hypodermoclysis the slow absorption, the entrance of some of the electrolyte into the cell and its elimination in the urine resulted in a negligible increase of this ion in the serum. Because the electrocardiogram depends chiefly on the serum potassium level the effects on the electrocardiogram were frequently slight or absent.

In 2 patients with more or less severe grades of myocardial damage due to coronary artery disease it was observed that the T wave inversion

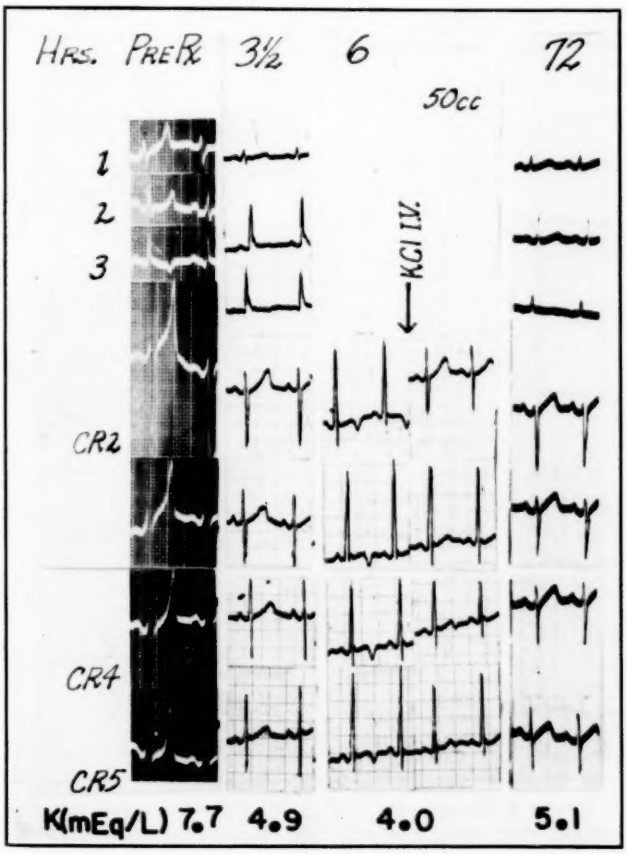

FIG. 3.—Electrocardiographic pattern in a patient before and after institution of therapy for diabetic acidosis and before the administration of isotonic potassium chloride. The figures in the upper part of the diagram record the hours after routine therapy was begun. The arrow indicates the time when isotonic potassium chloride was started. The pre Rx tracing (before therapy for diabetic acidosis was instituted) shows the tall T waves with a narrow base typical of hyperpotassemia. The serum potassium level at this time was 7.7 mEq./L., the CO_2 was 10 vol. %, the blood sugar was 520 mg. per 100 cc. Note the diminution in amplitude of the T wave 3½ hours after therapy was started following the administration of fluids and insulin. The serum potassium at this time was 4.9 mEq./L. At 6 hours note the inversion of the T waves. The serum potassium was 4.0 mEq./L. Following the administration of 50 cc. of potassium chloride note the change from an inverted to an upright configuration in all precordial leads. Final tracing taken 72 hours after beginning of treatment at which time the patient was able to take food by mouth. Note the return of tracing to normal. The serum potassium was 5.1 mEq./L.

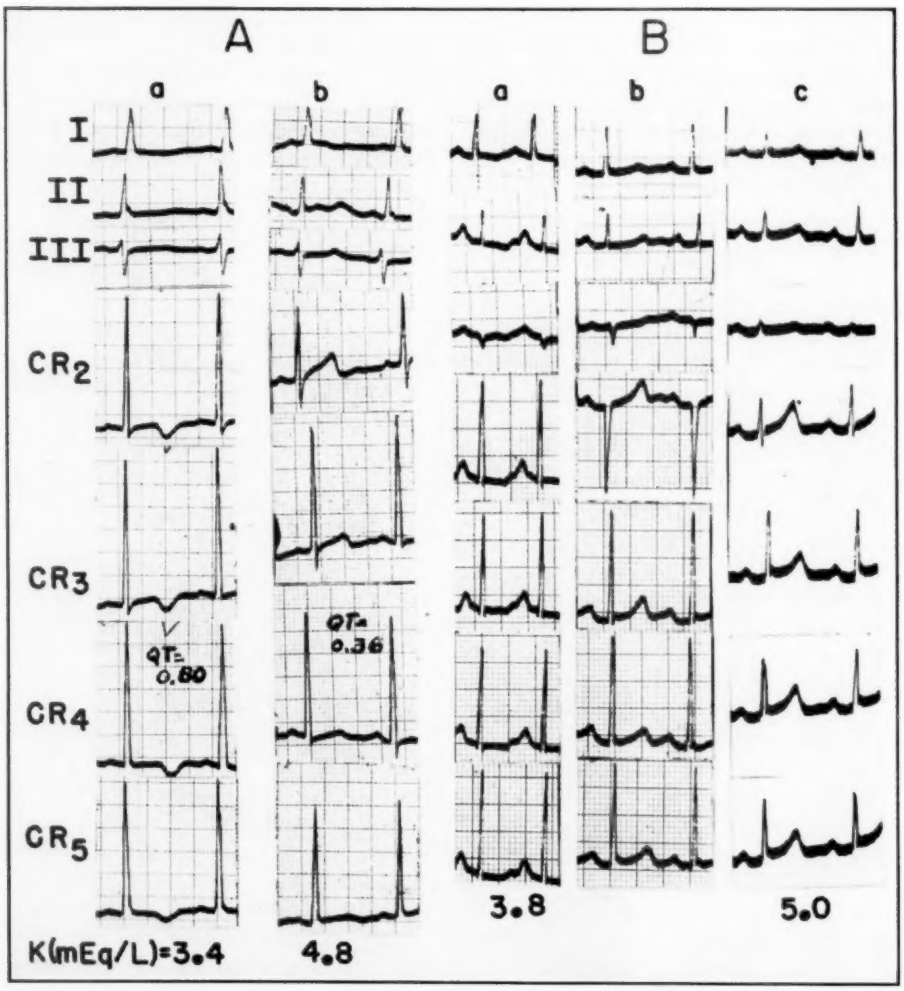

FIG. 4.—Pattern 2c. *(A)* J. M., age 45, was admitted with a diagnosis of acute pancreatitis and probably pyloric obstruction. He had been vomiting off and on for 3 weeks and took very little food by mouth during this time. He appeared rather weak and asthenic on admission. a, Note inversion of T wave and lengthening of QT segment which is particularly marked in the precordial leads. The QT segment measures 0.50 sec. (normal for this rate 0.36 sec.). b, Note upright configuration of T wave with shortening of QT interval 4 hours after 700 cc. of isotonic potassium chloride. The serum potassium at this time was 4.8 mEq./L.

(B) Patient, 87 years of age, was admitted with lower intestinal obstruction due to carcinoma of the sigmoid. a, Control tracing taken 2/2/48. Note inversion of T waves in all leads and lengthening of the QT interval. The serum potassium level was 3.8 mEq./L. b, Note upright T waves 2 hours after 300 cc. of potassium had been given. c, 2/7/48, after patient had begun to take food by mouth, note return of T wave and QT intervals to normal. The serum potassium level at this time was 5.0 mEq./L.

and ST segment depression tended to become more marked following potassium administration. This was probably the result of the potassium effect upon the damaged heart muscle with preponderance of its effect on the subendocardial portion of the left ventricle. Similar changes were observed by us in dogs, and by Sharpey-Schafer in

TABLE 2.—INCIDENCE OF ELECTROCARDIOGRAPHIC PATTERNS IN VARIOUS ETIOLOGIC STATES WITH HYPOPOTASSEMIA

Group	*No. of Cases*	*% of Cases*	*No. with U Waves*	*% of Group with U Waves*
A. *Diabetic Acidosis*				
I	9	25.7	2	5.7
II	21	60.0	8	22.8
III	3	8.4	1	2.86
IV	0	0.0	0	0.00
V	0	0.0	0	0.00
no QT prolong.	2	6.0	2	2.86
Totals	35	100.1	13	34.2
B. *Vomiting due to Intestinal Obstruction*				
I	17	53.0	11	32.4
II	8	23.5	4	11.8
III	2	5.9	1	2.9
IV	4	11.8	4	11.8
V	3	5.9	3	5.9
Totals	34	100.1	23	64.8
C. *Miscellaneous Group*				
I	6	60.0	5	50.0
II	2	20.0	0	0.0
III	1	10.0	1	10.0
IV	1	10.0	1	10.0
Totals	10	100.0	7	70.0

man, following potassium administration in the presence of myocardial infarction.

Discussion. That alterations in the serum potassium profoundly alter the electrocardiogram is not surprising. This electrolyte is intimately connected with the contractile process. Potassium is essential for normal muscular function. Potassium is essential also for normal nerve function, particularly in the neuromuscular transmission of the impulse. It acts in initiating the excitation process. Smith[29] has observed that dogs which were fed on a diet low in potassium developed paralysis of various muscle groups and unless potassium was administered, a state of collapse and death followed. Deficiency of body potassium has produced necrosis of heart muscle in the experimental animal[9].

The syndrome of hypopotassemia was initially studied in the human subject in familial periodic paralysis[30, 31]. There it has been observed to result in weakness, poor muscle tone, paralysis, and ultimately death. The following cardiac effects during hypopotassemia have been noted: dilatation of the heart, the development of systolic murmurs, ectopic rhythms and profound electrocardiographic changes of a type associated with severe grades of myocardial abnormalities. In addition, the blood pressure is usually low. These alterations are usually promptly reversed by the administration of potassium.

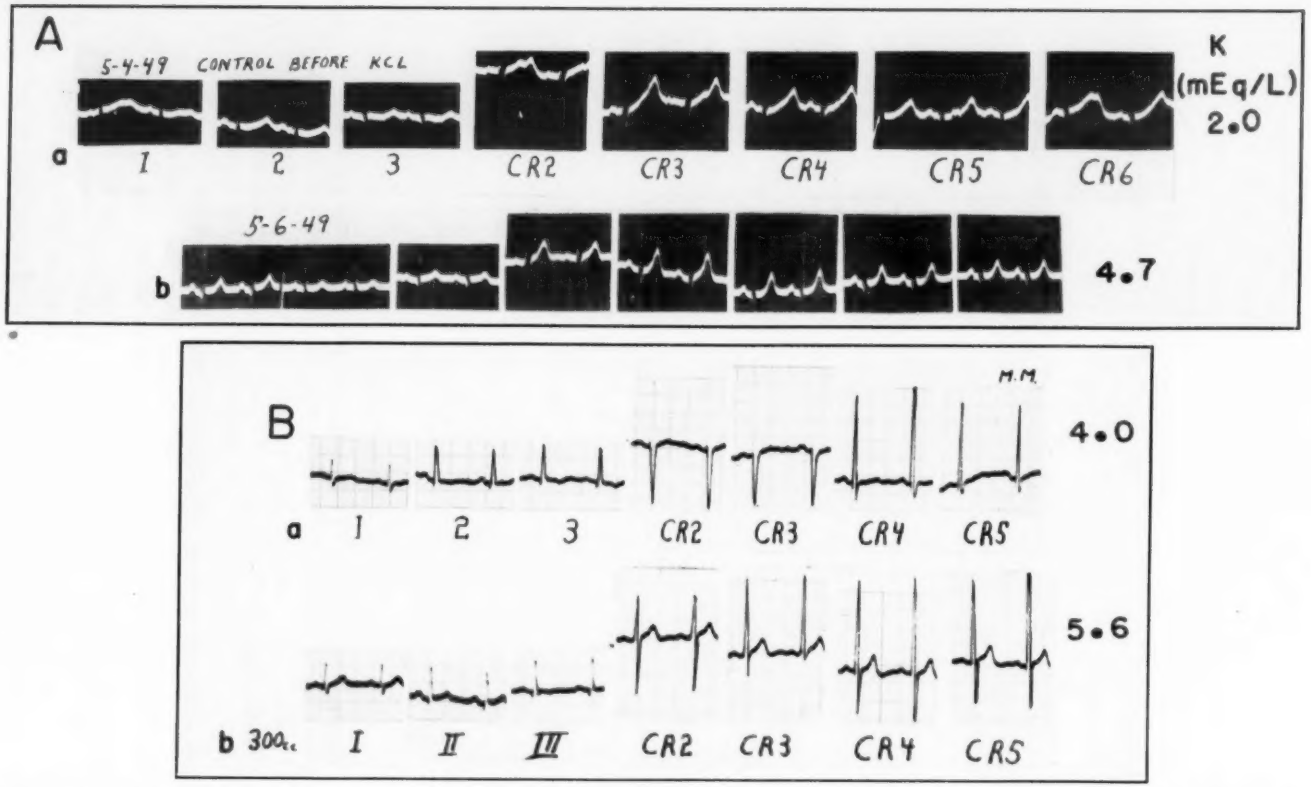

FIG. 5.—*(A)* M. B., female, white, age 54, had been vomiting for 6 days due to alcoholic gastritis. Upon admission this patient was in a moderate grade of shock. a, Control electrocardiogram. Note prolongation of QT interval and normal amplitude T wave best shown in precordial leads (Pattern 3a). The QT interval measures 0.44 sec. (theoretical QT for this rate is 0.31 sec.). The serum potassium level was 2.0 mEq./L., calcium 9.2 mg. % and pH 7.52. b, Note return of electrocardiogram to normal. The QT interval is normal and the T wave is of normal amplitude. The serum potassium level was 4.7 mEq./L., calcium 8.8 mg. per 100 cc., pH 7.41.

(B) Illustrates Pattern 4. M. M., male, white, 54 years of age was admitted to the hospital 3/23/49 with a history of vomiting for 3 days due to a small bowel obstruction. a, Control electrocardiogram taken 3/26/49. The T waves are flattened and the QT interval is prolonged measuring 0.40 sec. (theoretical QT 0.30 sec.). The serum potassium level was 3.5 mEq./L. b, Note normal QT segment, normal amplitude of T wave and disappearance of U wave 2 hours after 300 cc. of potassium chloride intravenously. The serum potassium level at this time was 6.2 mEq./L.

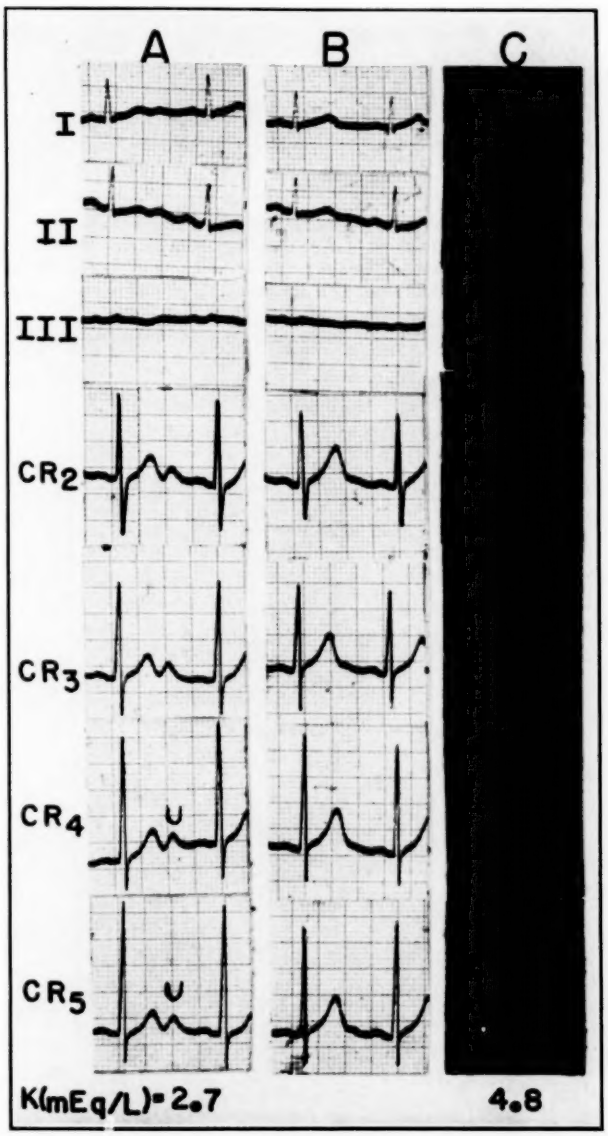

FIG. 6.—Pattern 5. C. W., male, white, age 25, had been vomiting for 1 day prior to admission. He was admitted with a diagnosis of duodenal ulcer. This patient was given saline and glucose parenterally but was unable to take food by mouth. a, Taken day following operation shows tall U wave following the T wave, best seen in precordial leads. QU wave measures 0.44 sec. (normal QT for this rate is 0.36 sec.). The serum potassium was 2.7 mEq./L. b, Note increased amplitude of T wave and shortening of QU interval 1 hour and 40 minutes later, after 500 cc. of isotonic potassium chloride had been given. c, 2/10/48 after patient had been taking food by mouth for 24 hours. Note normal configuration of T wave and normal QT interval. Serum potassium level at this time was 4.8 mEq./L.

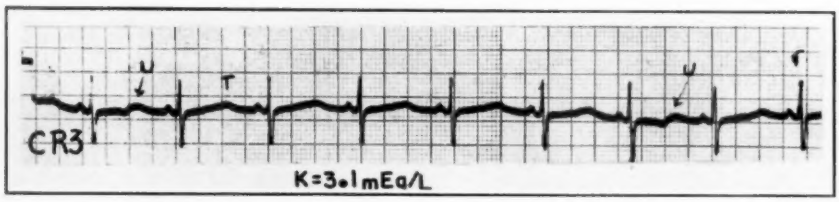

FIG. 7.—Patient with hypopotassemia (serum potassium level 3.2 mEq./L) who had been receiving adrenocorticotrophic hormone. CR2 showing successive cycles with QT interval prolongation and others with inverted T wave followed by a U wave. Note that length of QT segment and QT interval are identical.

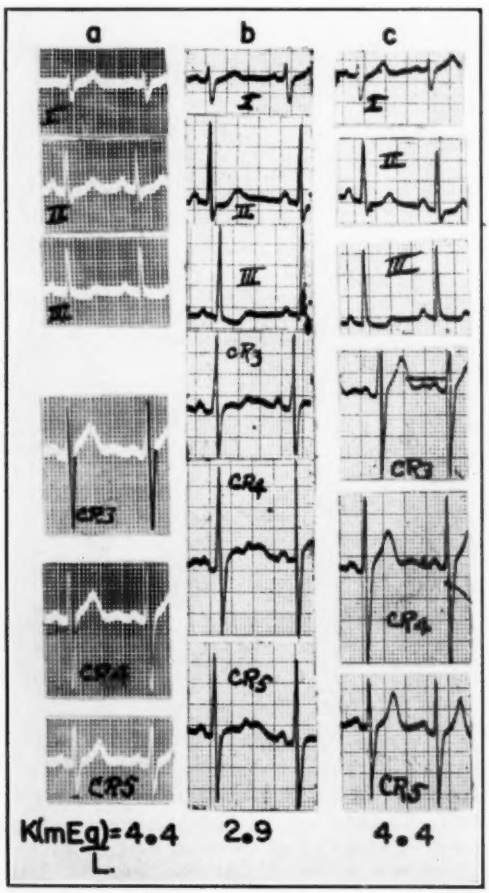

FIG. 8.—A. L., age 16. Familial Periodic Paralysis. a, Control before induction of attack. The serum potassium was 4.4 mEq./L. b, 2½ hours after induction of attack. Patient had typical evidence of periodic paralysis. Potassium was 2.9 mEq./L. Note lengthening of QT interval with change in T waves and presence of prominent U wave. c, Five hours after induction of attack. After 200 cc. of isotonic potassium chloride had been given by mouth and 500 cc. by clysis, electrocardiogram had returned to normal. The paralysis had disappeared. The potassium was 4.4 mEq./L.

The QT, QU Segment and Electrical Systole. The QT segment has been accepted by most cardiologists as a measure of electrical systole. This is not to be confused with mechanical systole. For practical purposes, the length of electrical and mechanical systole is almost the same when the QT interval is normal. When the QT interval is prolonged, the second heart sound appears an appreciable interval before the end of the T wave, indicating that in such a case electrical systole is often considerably longer than mechanical systole. The terminal portion of the QRST complex occurring after the second sound is due to electrical activity occurring after mechanical systole. This is often of considerable duration and may be composed of the terminal portion of the T wave and occasionally a U wave.

Whether electrical systole terminates with the T wave or U wave, if this is present, has been the subject of some discussion among physiologists. The U wave of the electrocardiogram has been observed and commented upon originally by Einthoven[10] and subsequently by other investigators[20,24,26,27]. Most of the studies have been made from limb leads, relatively few from the precordial leads. It has been stated that U waves of small amplitude, 1 to 2 mm., may be a normal finding. U waves of greater prominence and inverted T waves are said to be the result of myocardial disease. The subject of U waves and other waves occurring close to but soon after the T wave has received relatively little attention and little definite data are available concerning their significance. It has been said that the U wave represents a period of supernormal recovery and it is at this time that the ventricle is subject to the development of ectopic rhythm; experimentally the heart at this period responds to stimuli of less intensity than at other periods of diastole.

Einthoven[10] suggested that the U wave was due to an abnormal duration of ventricular systole in a damaged heart. Subsequently, Einthoven found the U waves in electrocardiograms of normal subjects and concluded that the wave indicated the persistence of contraction of some fibers during early diastole. Recently Erlanger and Gasser's[12] work on nervous activity has revealed the existence of after potentials, the duration of which far exceeds the period of excitation accompanying the propagation of the impulse. Such potentials are associated with the various stages of the recovery process. Nahum and Hoff[24] concluded that the U wave is to be regarded as part of the ventricular complex representing the location of the supernormal period. As a result of their investigations, these authors concluded that "The usual concept that the end of the T is the end of the electrical cycle is no longer tenable."

The presence of a U wave in patients with hypopotassemia is deserving of some comment. The U wave often appears immediately after the T wave, before the downward stroke has reached the base line; in other cases the wave appears after the T wave is completed and then is usually of considerable prominence.

In hypopotassemia 2 types of electrocardiographic alterations were observed in the QT or QU interval: 1, prolongation of the QT interval proper (observed in most of the patients); 2, relatively normal or slightly prolonged QT interval following a prominent U wave (observed in a smaller group).

That the QT and QU interval probably measure the same electrical events is suggested by the following: *a*, In Fig. 5, taken from a patient with hypopotassemia (CR2), consecutive cycles

show prolongation of the QT segment and a short QT followed by a U wave. The QT and QU length in these cycles are identical. *b*, Following potassium administration (Fig. 8) to a patient in whom a prominent U wave with a relatively normal QT was present, the U wave disappeared with little change in the T wave proper; the resultant effect was similar to that observed on a prolonged QT interval.

From the evidence presented above as well as the data observed in our cases, it might well be that in patients with hypopotassemia the QT or QU interval may be used interchangeably for diagnostic purposes and probably as a measure of electrical systole.

The Electrocardiogram as a Criterion of Hypopotassemia. The electrocardiogram is an important criterion of hypopotassemia. Although it is not a substitute for chemical estimation of this ion, combined with the history of diabetic acidosis, fluid loss by vomiting, diarrhea, and colitis, it has proven in our hands to be an important adjunct in the diagnosis of hypopotassemia. The recognition that 5 different patterns may be present as a result of a deficiency of this electrolyte should be of added importance. It should be noted, too, that in 80% of patients the electrocardiographic alterations consisted of ST segment depression and T wave inversion accompanied by prolongation of the QT interval (Patterns 1 and 2). In order of their diagnostic importance the alterations arrange themselves as follows: 1, QT interval prolongation; 2, T wave inversion and ST segment depression; and, 3, presence of a prominent U wave. The configuration of the T wave and ST segment may be of some help in differentiating between the presence of a previous diabetic acidosis or alkalosis accompanied by fluid loss; Pattern 2 was observed more often in the former group, Pattern 1 in the latter. Finally, the electrocardiogram is of help in following the effects of potassium administration and particularly in noting early effects.

Is there a relation between the electrocardiographic changes in hypopotassemia and the level of the serum potassium? We found that the QT interval prolongation was a crude guide of the degree of hypopotassemia. The T wave and ST segment changes were not a reliable criterion of the degree of hypopotassemia when comparisons were made in different patients; however, in the same patient, the similar T and ST changes were a fair guide of the degree of hypopotassemia on repeated correlation studies.

Conditions Simulating Electrocardiogram of Hypopotassemia. As to the electrocardiographic criteria of hypopotassemia, it should be noted that prolongation of the QT segment together with alterations of the T wave and ST segment may be observed in certain other clinical states. Among these are hypocalcemia, anoxia as observed in coronary occlusion, pulmonary embolism and shock-like states, hypertension, myocardial damage of certain types, the effect of drugs, particularly quinidine, and certain other unknown factors. The relative incidence of hypopotassemia as a cause of these changes bulks large and is the most important member of this group, as was observed in a series of 100 cases of QT interval prolongation, to be reported elsewhere[3]. The differential diagnosis can be made in most instances from the history and physical examination. The estimation of serum potassium is the final criterion. We have been able to make a diagnosis of hypopotassemia from the history and electrocardiographic findings, later confirmed by the chemical study in about 95% of our patients.

The electrocardiogram is of additional help in differentiating between the QT segment of hypocalcemia and hypopotassemia. In hypocalcemia there is an isoelectric period between the end of the S wave and the beginning of the T wave; the T wave proper is unaltered by the hypocalcemia. In hypopotassemia the T wave itself is altered by the production in most instances of an ST segment depression or a T wave inversion, and the QT interval prolongation involves the entire QT segment. In occasional cases the differential diagnosis is difficult to make from the electrocardiogram alone. The electrocardiogram is of help in differential diagnosis of other conditions producing QT segment prolongation. These will be discussed in a subsequent report[3].

Electrocardiographic Effects of Other Electrolyte Alterations in Association with Hypopotassemia. It must be recognized that in many instances hypopotassemia exists in association with other electrolyte changes that could conceivably alter the electrocardiogram. In diabetic acidosis, alteration in sodium, phosphate and the serum magnesium are occasionally involved; in cases of fluid loss due to vomiting alterations in sodium, phosphate and occasionally calcium may exist.

As far as we are aware, sodium and phosphate, *per se*, do not affect the electrocardiogram. Little is known as to magnesium effects. Of these electrolytes, only calcium is known to affect the T wave and QT interval. In diabetic acidosis the calcium values were abnormal in relatively few cases; in vomiting patients, the total serum calcium was diminished in only 3 patients; the question of a reduction in the ionizable fraction in alkalosis is as yet not settled.

We have found, however[6], that the administration of potassium alone will revert the electrocardiogram to normal in spite of the coexistence of other electrolyte abnormalities. The only exception to this is in the presence of combined hypocalcemia and hypopotassemia, where it is necessary to administer both calcium and potassium in order to restore the electrocardiogram to a normal configuration.

However, the possibility should be considered that the existence of coincident multiple electrolyte deficiencies may alter the speed or sensitivity of the response to potassium administration.

Summary. 1. The subject of hypopotassemia is of considerable importance because of the frequency with which it occurs and the profound nature of the disturbances of body function that exist during this state. The importance of the electrocardiogram as an aid in the diagnosis of hypopotassemia and in following the effects of therapy is stressed.

2. The electrocardiographic patterns observed in hypopotassemia of various etiologies in 79 patients are presented. Five different patterns of T and ST segment changes accompanied by QT segment prolongation were observed. These consisted of the following: 1, depression of the ST segment of varying degrees; 2, inversion of T waves; 3, T waves of normal amplitude with prolongation of the QT interval; 4, low amplitude of T wave; 5, prominent U wave following T wave. The first 2 patterns constituted the changes shown by 80% of those observed. Pattern 1 was observed most frequently in vomiting cases, Pattern 2 in diabetic acidosis.

3. The electrocardiographic alterations observed in hypopotassemia were immediately reversible following the administration of potassium.

4. The U wave is an important criterion of hypopotassemia, having been present in 33 cases (42%). The signifi-

cance of the U wave generally and its relation to electrical systole is discussed. Evidence is presented which suggests that lengthening of the QT or QU interval are both important in the diagnosis of hypopotassemia.

5. In some instances of alkalosis a diminished serum or ionizable calcium probably contributed to the electrocardiographic changes. The effect of the administration of this electrolyte suggested that its role in the production of the electrocardiographic alterations was a minor one.

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CEREBRAL ANGIOGRAPHY

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PRIOR to the advent of radiography, the clinical diagnosis of intracranial lesions depended almost entirely on an evaluation of the patient's history, symptoms and signs. In the hands of the most astute and experienced neurologists, such limitations permitted only a very tentative diagnosis and in most instances confirmation of the diagnosis necessarily awaited autopsy. Thus it was that little impetus was given to cranial neurosurgery.

With Roentgen's recognition of the X-ray and the practical technical developments which rapidly followed, it soon became possible to obtain quite satisfactory radiographs of the skull and its contents. This immediately clarified to a great extent many of the problems which had previously faced the neurologist and it was quickly appreciated that intracranial pathology could in many instances characteristically manifest itself radiographically in one or more of several ways such as 1, directly or indirectly destroying the normal bone architecture of the skull; 2, displacing normally calcified intracranial structures such as the pineal body and the choroid plexuses; and 3, by laying down within the lesion substances which are opaque to Roentgen-rays. With this new tool, the accurate diagnosis of many of the diseases of the brain and its envelopes became practicable. The natural result of accurate diagnosis was a desire for definitive treatment and the necessary stimulus for the development of neurosurgery was thus provided.

It was not long, however, before it became clearly evident that a large proportion of intracranial lesions failed to produce any roentgenological

changes in the skull whereby the existing lesions could be detected. In an effort to make diagnosis possible in this rather large group, Dandy in 1918 after observing the striking changes present in a patient suffering from traumatic pneumocephalus, withdrew the cerebrospinal fluid from the ventricles and replaced it with a gas. The ventricular cavities thus became relatively radiolucent in comparison to the surrounding brain substance and could thereby be visualized on subsequent Roentgen-ray examination. A study of the distortion and, or, displacement of the ventricular system proved to be a vital factor in localizing and often diagnosing those space occupying processes which otherwise were roentgenologically undetectable.

Dandy's work proved to be a most valuable aid to the neurological examination of the encephalon and contributed immeasurably to the rapid progress that neurosurgery has made since its publication. Indeed, many feel that Dandy's contribution is perhaps the greatest single advance which has as yet occurred in the evolution of the neurological examination.

Although standard and contrast roentgenographic examination of the cranium (ventriculography and encephalography) had successfully clarified many of the diagnostic problems associated with intracranial disease, there still remained a sizeable group which consistently escaped detection by these methods. This was particularly true of those lesions which were directly a part of or intimately associated with the vascular system of the brain and meninges. It was to this problem that Egas Moniz of Lisbon, Portugal, first turned his thoughts in the early 1920's. He conceived the idea that if the blood vessels of the encephalon could be made temporarily opaque to the Roentgen-ray, then their intrinsic and pressure abnormalities might be discerned. Moniz's early efforts concerned themselves with the injection of opaque material into the cerebral vessels of cadavers. His first notable encouragement came when he succeeded in correctly diagnosing a temporal lobe tumor from Roentgen-ray films made of the opacified vessels prior to autopsy. Moniz then practiced his new technique on dogs and finally on living humans. His first paper on cerebral arteriography appeared in 1927[4] and since then he has continued to work towards the perfection of his methods. During this period he has published several fundamental books and many articles[5,6,7] on cranial angiography and might rightfully be termed the father of that technique.

Cerebral angiography was quickly taken up by other workers in Europe and many contributions appeared in European literature during the 1930's[3, 22,28]. It was not until the late 1930's and early 1940's that interest in this field manifested itself in North America, first in Canada[8,29] and later in the United States[12]. In the past few years, cerebral angiography has found its deserved place in this country and is now widely used in almost all teaching institutions and many smaller hospitals.

Cerebral angiography finds its most important use in the detection of lesions intimately associated with the blood vessels. Thus it is that such conditions as aneurysm, arteriovenous fistula, thrombosis and angiomatous tumor can be clearly visualized by this technique. In addition many other pathological states, including almost all the tumors as well as non-neoplastic space-occupying masses such as hematoma, may be demonstrated and not infrequently a correct cellular diagnosis may be suspected.

In no way should cerebral angiography be considered a competitive ex-

amination in respect to ventriculography or encephalography. Instead, it is a complementary study. It is believed by most that arteriography should be used in patients in whom a a vascular lesion is suspected and in all others in whom air studies fail adequately to demonstrate a presumed lesion. In the examination of patients who possibly harbor a space-occupying intracranial mass and who have a markedly elevated cerebrospinal fluid pressure, cerebral angiography is the study of choice because, unlike ventriculography and encephalography, it affects only slightly the pressure relationships existing within the skull. Inasmuch as only a very few advocate the bilateral injection of the cerebral vascular system with opaque material[7], it is necessary to determine on which side of the brain the pathological process lies. Only rarely will injection of the opposite side yield any useful information.

The use of both air study and cerebral angiography has been advocated by some. This however is apt to be a quite disturbing procedure to the patient, and, in our experience and that of others, it frequently leads to a confusing picture. It appears that more reliable information can be obtained by conducting the studies separately.

Like all diagnostic tests, cerebral angiography has its contraindications. These may be grouped in 2 large categories which stem from the facts that 1, objectionable sequelae, usually depending upon toxicity or an intrinsic sensitivity to the contrast material, may follow its injection, and 2, the cerebral vessels of a patient may be so damaged by disease or the aging processes that the sudden rise in intravascular pressure occurring during the necessarily rapid injection technique, may produce further impairment of those vessels and the brain substance which they supply. Thus it is deemed wise to withhold cerebral angiography from those patients who are in the acute stage of a vascular accident and those who have advanced arteriosclerosis, extreme hypertension or cardiac decompensation. In the case of an individual with known sensitivity to a given contrast substance, the examination is contra-indicated as far as that chemical is concerned. It may be safely done, however, by substituting another contrast medium of a chemical family different than that of the offending agent.

The technique of injection as first recommended by Moniz[5] and still widely used, necessitates surgical exposure of the vessel to be injected. This procedure has much to be said for it, as by its use there is little chance of extravasation of the opaque medium, the desired branch (internal, external or common) of the carotid artery may be chosen, the artery may be occluded proximal to the point of injection, thus preventing dilution of the medium, the head may be more conveniently placed for the radiographic filming and there is little danger of injuring or stimulating the carotid body. There are, however, several disadvantages to this technique. These revolve about the fact that the surgical exposure of either the carotid or vertebral artery necessarily requires aseptic technique and facilities and it is a time consuming procedure. Careful aftercare is most important to prevent bleeding into the adjacent tissues which occasionally may be of alarming proportions. Infection of the exposed tissues, as in any surgical procedure, must be guarded against.

It is possible by means of the percutaneous route to inject either the carotid or vertebral arteries without surgically exposing them. This so-called blind technique has been de-

scribed by several authors[11]. Although it may at first appear difficult, it can be mastered in a relatively short time, as is exemplified by the combined experience of a changing group of neurosurgical house officers at the Johns Hopkins Hospital. During 1948, 113 percutaneous carotid injections were attempted, and in these there were 18 failures. In 1949, the percutaneous route was tried 112 times and led to successful results in all but 6 instances. During the first 2 months of 1950, 43 carotid angiograms were done using percutaneous injection, and in this group there were no failures. Our results in percutaneous vertebral injection have not been as encouraging probably because the vertebral artery is smaller than the carotid and it is more deeply buried and also because of the fact that we have had little opportunity to acquire sufficient skill, as there is comparatively little clinical demand for vertebral arteriography. In 1948 there was one attempt and this was unsuccessful. In 1949 there were 14 trials, of which 5 were in vain. In January and February of 1950, three patients were tried with success in only one. Thus, as the percutaneous method of puncturing the carotid and to a lesser extent the vertebral artery, is quite simply executed, requires little time, surgical facilities or aftercare, it is being more and more widely used in preference to the open procedure. There are however a few difficulties inherent in the percutaneous method. As noted above, it is not always possible to enter the artery, particularly in those individuals who have short stocky necks, and even after the artery is pierced, considerable care is required to maintain the needle tip within the lumen of the vessel. Failure to do so of course may result in extravasation of the opaque material into the soft tissues of the neck. This is an occasional and undesirable happening, as the contrast media available for cerebral angiography are either very irritating to tissue or are radioactive[14]. Another and less serious objection to the percutaneous method is the fact that once the needle is inserted into the artery, very little motion of the patient's head is permissible, which increases the difficulties of positioning the head for radiography.

A contrast medium, to be ideal, must satisfy several rigid conditions: 1. It must be innocuous to the patient. This means that there should be no toxic or anaphylactic reactions to the body as a whole and also that there be no undesirable local effects at the site of injection. In cerebral angiography, the injected material is carried immediately to the brain and thus is capable of exerting its effects in high concentration upon the brain in general and the vital centers in particular. Thus, many substances which are useful for peripheral or cardiac angiography cannot be used for either carotid or vertebral injection.

2. It must be rapidly excreted from the body or be entirely inert if retained. This ordinarily requires the substance to be one which can pass through the kidney in concentrations sufficiently low to avoid damage to this organ, or one which can be stored in the body tissues in an innocuous state.

3. It must, and this is very important, be relatively opaque to Roentgen-rays and thus afford good contrast in comparison to the surrounding brain substance and skull. It is not enough to outline only the major vessels and their tributaries; indeed, it is frequently necessary to visualize the detail of a vascular pattern consisting of a network of tiny vessels. Unless this network be filled with a contrast substance of considerable density, its

image will not be demonstrable on the film.

4. The final essential is that it be readily miscible with the blood. Should the substance act like an oil and fail to mix well, then the entire lumen of the vessel will not be filled with opaque material and the roentgenograph of this vessel will unavoidably represent a distorted image.

Inasmuch as it has long been known that the absorption of Roentgen-rays is a function of the atomic number, early attempts to find a good contrast substance were directed to the higher elements in the periodic table. Thus, it was that Moniz began by trying several of the halogens in combination with other substances which in themselves might be more or less opaque to the passage of Roentgen-rays and which, in combination with the halogen, provided a chemical which was relatively non toxic to the body. Moniz first used strontium bromide in 70% aqueous solution but soon found this compound to be objectionably injurious. After experimenting with several other substances, he found 25% sodium iodide to be a satisfactory medium and used this material until 1931 when he changed to thorotrast.

The contrast media in use today are of 2 types: organic iodine compounds and thorium dioxide solution.

Diodrast, the commonly used name for 3,5 diiodo-4-pyridone-N-acetic acid diethanolamine, is a representative member of the organic iodine family. (There are also neoiopex, perabrodil, and others.) Diodrast is an aqueous solution containing about 50% iodine in firm combination. Though far from ideal, it does reasonably satisfy most of our requirements. It is readily miscible with blood and it is excreted rapidly by the kidneys. Indeed diodrast finds its widest use as a contrast substance for intravenous pyelography. Diodrast, however, is toxic both generally and locally. General reactions may be immediate or delayed. In the first instance they are apparently due to the direct action of the drug on the cerebral centers or to an anaphylactic response to the chemical. They manifest themselves by a transient subjective sensation of heat, increase in pulse rate, fall in blood pressure, respiratory distress, nausea and vomiting, transient aphasia and hemiplegia, convulsions, coma and occasionally death. Allergic phenomena may also appear in the form of urticaria, lacrimation, rhinitis, and edema of the tongue, glottis and larynx.

Several tests for diodrast sensitivity have been advocated. These include such procedures as the instillation of a drop of diodrast in the conjunctival sac, and the subcutaneous or intravenous administration of small amounts of the drug. In the Author's opinion none of these tests are foolproof since he has seen numerous minor, several major, and fortunately only a few fatal, reactions following the use of diodrast in intravenous urography, angiocardiography, and cerebral angiography in patients who failed to show any demonstrable response to the sensitivity test. In defense of diodrast, it can be said that all the fatal reactions in the Author's experience, with the possible exception of one, have occurred after the injection of 70% diodrast for angiocardiography. However, death as a response to the 35% solution has been many times reported in the literature[23]. In cerebral angiography, 70% diodrast will almost always cause a severe central reaction and it thus should never be used for this study. Some workers have reported satisfactory results with a 50% solution, but this has not been the universal experience[13].

In this hospital, during the years

1948 and 1949 and the first 2 months of 1950, there have been 234 patients who had cerebral angiograms performed via the percutaneous route with 35% diodrast. Several of these cases had multiple examinations. There have been only 7 complications, of which 6 were transient and left no permanent residuals. The seventh, which was fatal, occurred in a comatose woman with severe hypertension and clinical evidence suggesting an intracranial hemorrhage. In retrospect it seems rather foolhardy to have attempted to perform an angiogram on this patient and in the light of our present feelings, cerebral arteriography would not be considered for a patient in such poor physical condition.

Diodrast also has an unpleasant local reaction and patients often complain of a burning pain along the course of the injected vessel. This is undoubtedly due to the spasm which diodrast initiates. Although the pain is not intolerable, spasm of a vessel can frequently detract considerably from the interpretability of the subsequent films and may occasionally lead to an incorrect diagnosis. If diodrast is permitted to escape into the perivascular tissues, it unfortunately may cause a reaction which at times can be sufficiently severe to produce local necrosis.

The radio-opacity of diodrast (35%), though not as great as some other substances (thorotrast) available for cerebral angiography, is still sufficient to demonstrate adequately both the arterial and venous systems of the intracranial circulation even in their fine ramifications.

Colloidal tri-iodo-ethyl stearate, another iodine containing organic drug, was used rather extensively in Europe prior to the second World War for cerebral arteriography but it has never been introduced into this country. It is reported that this material has better contrast than diodrast (about the same as thorotrast) and its viscosity and miscibility are such that it easily penetrates even the tiniest vascular channels. In addition, tri-iodo-ethyl stearate is said to be rapidly excreted, to have a low toxicity, to produce very little if any spasm of the injected vessel, and if extravasation occurs little pain or tissue damage results[2,15]. If the above reports prove to be correct, then tri-iodo-ethyl stearate would certainly very closely approximate our ideal contrast medium. However, the Author can neither confirm nor deny this possibility as he has had no experience with this drug nor is he aware of anyone in North America who has. Attempts to obtain the material from Europe or to synthesize it here have been to no avail.

The second contrast medium used rather widely in cerebral angiography is a 25% colloidal solution of thorium dioxide marketed under the name Thorotrast. Thorium has an atomic number of 90 and is therefore quite opaque to Roentgen-rays. In the usual concentration permissible for angiography, vessels filled with thorotrast cast a denser shadow than do those containing diodrast or other iodine compounds[14], and the subsequent angiograms presents a more readily interpretable appearance.

Thorotrast is less irritating locally than is diodrast and the injection is therefore usually painless. The general reactions of thorotrast (anaphylactic or other) are also less pronounced than those which occasionally follow the injection of an iodine containing substance. They do occur, however, and present much the same clinical form. Deaths have been reported following thorotrast injection[26].

As mentioned above, thorium has a high atomic number and thus lies within the group of naturally radioactive

elements. Its half life is 1.31 x 10^{10} years; in its decay it emits alpha, beta and gamma rays. The biological effects of the beta component are almost insignificant. However, the amounts of alpha and gamma radiation are appreciable. Twenty-five cc. of thorotrast emit alpha particles equivalent to 0.5 to 1 microgram of radium and gamma rays equivalent to 0.3 to 0.4 micrograms of radium. Since studies in radium poisoning in radium watch dial painters have indicated that radium in amounts as small as 0.5 micrograms may be very dangerous[18], the potentiality of serious consequences following the use of thorotrast becomes paramount. If thorotrast were excreted from the body as rapidly as are the iodine compounds then it would be permissible to disregard thorotrast's radio activity. Unfortunately, just the reverse is true, as thorotrast is actively taken up by the reticulo-endothelial system and deposited in high concentration in the liver, spleen and bone marrow where it is retained for long periods of time. It has been experimentally shown that thorotrast can be detected in the reticulo-endothelial system within 5 minutes after injection, and decay products of thorium have been found in the feces and expired air of patients as long as 7 years after injection of thorotrast[27]. List, Burge and Hodges[16] ashed blocks of liver spleen and bone from an individual who, 2 months previously, had received 44 cc. of thorotrast. Measurements of the samples showed that the amount of radioactivity in the spleen and liver exceeded the lowest recorded level in cases of radium poisoning. Since the above authors ordinarily use only 30 cc. of thorotrast, they adjusted their figures accordingly and concluded that in the usual case the amount of radioactivity present in the reticulo-endothelial system would fall below that of radium poisoning. However, the amount present would still be quite large and would seem to present a severe hazard.

The effect that retained thorotrast has on the body has been discussed at considerable length in the literature. That it is or is not sufficiently harmful to preclude its use is not universally decided. The chief hazard is of course the possible carcinogenic effect of radioactive materials in general. It has been demonstrated by Selbie[25] that thorotrast is capable of producing sarcomata when injected beneath the skin of rats and mice. Indeed, he has been able to produce sarcoma in rats in 85% of the animals injected. However, the quantity of thorotrast which he used was quite large and therefore not strictly comparable to the situation prevailing after the intra arterial injection of the usual amounts of thorotrast for cerebral angiography.

A search of the literature reveals only 1 report of a malignant tumor which conceivably was related to the presence of thorotrast in the body tissues. This was recorded by McMahon, Murphy and Bates[19,20] in a 71 year old woman who died of a massive intra-peritoneal hemorrhage from a primary endothelial cell sarcoma of the liver. The patient had received 75 cc. of thorotrast 13 years previously for the purpose of outlining radiographically a gumma of the liver. At autopsy, thorotrast was found to be scattered throughout the liver. Immediately adjacent to the base of the tumor (apparently at the site of the healed gumma) there was a large collection of thorotrast. The tumor itself was composed of endothelial cells some of which had phagocytosed thorotrast particles. Thorotrast was also found in the bone marrow, spleen and lymph nodes. "In each of these, there was degeneration, atrophy and defective

growth. Much of the marrow was replaced by fat and the little hematopoetic tissue was represented by clusters of abnormally primitive cells."[19] There can be little doubt that the radioactive thorotrast in this patient's bone marrow had produced a deleterious effect. It also seems reasonable, although it certainly is not proven, that the thorotrast played an important part in the development of the endothelial cell sarcoma. It is of interest that this same case had been reported 3 years earlier[21] as an illustration of the diagnostic advantages of thorotrast.

In comparing the overall qualities of thorotrast and diodrast with a view of deciding which is the most suitable contrast medium, it is the Author's opinion that the lack of excretion combined with the radioactive nature of thorotrast are more serious objections than the relatively greater frequence of reactions that occur with the use of diodrast. Those who are currently employing thorotrast inject a maximum of approximately 30 cc. for one angiographic study. In our experience it is often desirable to repeat the examination in the immediate or even distant future, or to inject one or more of the other 3 vessels supplying blood to the brain; and if thorotrast were used, there would not infrequently be patients whose total dosage would far exceed what at present are possibly safe levels.

The radiographic component of cerebral angiography is most important because, regardless of optimum filling of the cerebral vessels with a good contrast material, if the quality of the roentgenograms are poor and the time of their exposure is improperly controlled, then the resultant films will be all but useless. The radiographic recording of a well injected cerebral angiogram requires utmost coordination between injector and Roentgen-ray technician, and precise teamwork is essential before routinely successful results are attained.

Radiographic equipment in use at most hospitals today leaves a great deal to be desired in regard to cerebral angiography, as multiple exposures in rapid succession are rarely permitted. Most workers have been thus forced into the position of obtaining only 3 films in one plane following one injection. If stereoscopic views are desired or if both lateral and anteroposterior projections are to be obtained, then multiple injections of contrast material are necessary. Recent technical developments have produced film transport mechanisms[24] designed to permit exposures in rapid sequence by means of either successively changing film cassettes or by simply intermittently advancing film through a roll camera type of apparatus. That multiple exposures following the progress of the opaque substance from the arterial tree through the capillary bed and on into the collecting venous channels are necessary has been demonstrated many times in the experience of the Author and others. On several occasions a film showing good filling of the cerebral vessels has failed to demonstrate a pathological lesion only to have it appear characteristically on other exposures made a fraction of a second before or after.

Although a few investigators take cerebral angiographic films in only one plane, it is generally agreed that exposures in 2 planes at right angles to each other are not only desirable but absolutely essential[9,14,16,17]. In order to accomplish this with present day commercially available equipment, 2 separate injections of contrast material each followed by a series of Roentgen-ray exposures must be accomplished. If stereoscopic views are desired, then 4 series of injections and films must be

made. Since the injection of contrast medium, regardless of its type, always presents a definite though small hazard to the patient, it has appeared desirable to us to devise radiographic equipment which will insure the desired films but at the same time will decrease the total amount of contrast material used. Thus we have recently designed and built a double film transport mechanism which in conjunction with 2 Roentgen-ray generators and 2 Roentgen tubes permits the making of simultaneous films in 2 planes. With this equipment it is possible to complete the desired radiographic studies with only 2 injections of contrast material. If non-stereoscopic films are sufficient, only 1 injection is necessary. The net result is that angiographic studies (cerebral, cardio or other) can be obtained with only one-half the volume of contrast media ordinarily required. It would be a further distinct improvement if simultaneous 2-plane stereoscopic films could be made with 1 injection. This, however, is a technical problem of considerable magnitude and as yet a satisfactory solution is not available.

There remains 1 additional portion of the radiographic equipment that needs technical attention. The quality of most angiograms is rather poor in comparison to standard radiographs. The chief cause of this lies in the fact that in most angiographic equipment a stationary grid of the Lysholm type is used. Since the efficiency of this kind of grid is low, a considerable amount of secondary radiation succeeds in reaching the film and thus partially clouds the desired image. In addition, since the grid is stationary, grid lines appear on the film. The remedy for these defects lies simply in the use of a more efficient grid of the moving type. As yet, such equipment is not commercially available, but it is expected that it soon will be.

Whether or not one chooses to expose surgically or to inject percutaneously the desired vessel, the injection itself must be done rapidly. This actual maneuver requires the application of considerable force to the plunger of the syringe, and it is difficult to apply manually the necessary constant pressure. Furthermore, since filming must begin at or just before the completion of the injection, the operator's hands must be protected from the cumulative damaging effects of both primary and secondary radiation. Protection with lead shielding is usually a cumbersome and inconvenient procedure, to say the least. To overcome these difficulties, we have constructed an automatic injection device which operates on a vacuum principle. With this apparatus the speed of injection can be preselected at will, and the operator's hands remain totally outside the field of radiation.

It is not the purpose of this paper nor does space permit a detailed discussion of the anatomy of the cerebral vessels and their related brain structures. Suffice it to say that the interpretation of cerebral angiograms, like the interpretation of roentgenograms of other parts of the body, requires an intimate knowledge of the anatomy involved. This is particularly true of cerebral angiography because very frequently the demonstrable deviations from the normal may be quite minute. An accurate knowledge of neuroanatomy may be gained from the literature and standard texts[9,11,14,16,17]. Unfortunately, however, this is not sufficient because the material available for study fails for the most part adequately to cover the many normal variations and anomalies. It has been the almost universal experience of the uninitiated that this aspect of the interpretation of cerebral angiography has

been the greatest stumbling block. The Author has recently had the good fortune to examine a manuscript which discusses in great detail the normal vascular anatomy of the brain and its many variations. This paper is soon to be published and will undoubtedly serve a most useful purpose[1].

The interpretation of cerebral angiograms depends upon a meticulous evaluation of the changes in the vascular system of the brain produced by the various pathological processes which may arise in or about those vessels. In general, these changes fall into one or more of the following categories: (a) displacement (b) abnormal caliber (c) delay in filling (d) delay in emptying (e) abnormal arterio venous communication (f) abnormal distribution and (g) the formation of new vessels[9,10,11,14,17].

Displacement of any one or more of the cerebral vessels depends to a large extent on the location of the space occupying mass rather than on its overall size. A small mass lying close to a vessel will ordinarily produce a more prominent effect than a large one placed at some distance. In addition, lesions which are apt to be contained within themselves, or are encapsulated, produce more vascular displacement than do those which are by nature infiltrative. The direction and amount of displacement as well as the portion of vessel or vessels affected make it possible to determine with a considerable degree of accuracy the location of a space-occupying mass in almost any part of the brain. Lesions in the temporal lobe perhaps illustrate characteristic displacement better than those in any other location. Here in the lateral view, the middle cerebral vessels are displaced upward and frequently anteriorly while the anterior cerebral is generally unaffected. In the anteroposterior projection, the middle cerebral group is displaced medially. Occasionally, if the mass is suffiicently large, the anterior cerebral artery is displaced away from the lesion.

The caliber of a vessel frequently is a diagnostic point in interpreting cerebral angiograms. This feature is particularly noticeable in such lesions as angiomata where the arteries and veins involved in the process may be several times normal size. The presence of aneurysm abruptly changes the caliber of a vessel and ordinarily appears as a small saccular projection arising from the side of a vessel, commonly the intradural portion of the carotid or the circle of Willis. Other processes such as thrombosis, arteriosclerosis and spasm may produce profound effect on the apparent size of the lumen of a vessel.

Delay in filling is not usually a very helpful sign. It may be seen in the presence of aneurysm or arteriovenous fistula. On the other hand, delay in emptying is frequently seen and is most important. The delay is usually caused by the abnormally large volume of dilated vessels or by the presence of abnormal vessels within a tumor mass. Thus, when the normal vessels empty, opaque material is retained in the abnormal channels and casts a definite shadow on the subsequent film. This is the so-called "tumor stain" and it is most beneficial in ascertaining the histological nature of a tumor (many tumors have a distinctly characteristic vascular pattern) as well as its physical size and location.

Normally there is of course a capillary barrier between the arteries and veins. There are, however, many pathological processes which change or circumvent this barrier. Thus, early filling of the cerebral venous system may be seen when such lesions as arteriovenous fistula and angiomatous or other tumors are present.

The normal distribution of the vascular system is occasionally disturbed by intracranial pathology. A striking example of this frequently occurs in association with meningiomata which often receive a portion of their blood supply from the external carotid artery by way of the meningeal vessels. Under these circumstances the meningeal vessels are distorted in shape and frequently enlarged in caliber. On occasion meningiomata have derived blood from the superficial branches of the external carotid which have perforated the skull.

The formation of new vessels by a tumor is a familiar pathological picture. Angiographically, these vessels are commonly demonstrated as large channels running from one or more of the major cerebral vessels to the tumor or small, even pin point pathways within the tumor itself. The size, shape, length and numbers of these new vessels can be of extreme diagnostic help particularly if one wishes to venture a histological opinion.

Summary. 1. The historical background and development of cerebral angiography have been recalled.

2. The indications and contraindications of cerebral angiography have been examined.

3. The various techniques for injecting the opaque material have been considered and, it is believed, ample justification for preferring the percutaneous route has been advanced.

4. The advantages and disadvantages of the several contrast media have been treated and the use of thorotrast has been condemned.

5. The radiographic equipment suitable for cerebral angiography now commercially available, and technical developments at the Johns Hopkins Hospital pertaining to experimental radiographic apparatus, have been considered.

6. The general principles of the interpretation of cerebral angiograms have been discussed and important diagnostic features have been pointed out.

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THERAPEUTICS

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AUREOMYCIN

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AUREOMYCIN represents probably the most important development in antibiotic therapy since the introduction of penicillin. Fortunately, like chloramphenicol (chloromycetin), it can be effectively administered by the oral route. The substance is elaborated by Streptomyces aureofaciens and was first described by Duggar[31]. It has been found to be bacteriostatic, as well as bactericidal, for a number of important gram-negative and gram-positive microbes. Furthermore, it has been shown that rickettsiae are sensitive to its action. In spite of early reports concerning its effectiveness against certain viruses, it would appear that as an antiviral agent it has considerable limitations which will be mentioned later. That aureomycin possesses considerable antispirochetal activity was evident from studies reported from the Mayo Clinic[42]. It is regarded by many as the treatment of choice in lymphogranuloma venereum, granuloma inguinale, herpes zoster and so-called primary atypical pneumonia. It is thought to be effective in the treatment of infections caused by Klebsiella organisms, Hemophilus influenzae and Pasteurella tularensis. It is said to have some value in the treatment of brucellosis. It is of considerable practical importance that many penicillin-resistant and streptomycin-resistant, as well as streptomycin-dependent, organisms are susceptible to its action. Aureomycin is a fairly soluble substance, but in solution it has a hydrogen-ion concentration between 4 and 5. According to Bryer and his colleagues[18], it deteriorates rapidly in alkaline solution. This being so, in the treatment of infections of the urinary tract it would seem highly desirable to attempt to keep the pH of the urine in the acid range.

ABSORPTION, DIFFUSION AND EXCRETION. Aureomycin is rather unstable in serum and body fluids, which property caused considerable difficulty in early studies on absorption, diffusion and excretion of the material. Heilman and I[44] carried out some studies on the general subject. Using the method developed in the laboratories of the Mayo

Clinic, we were able to establish certain facts concerning the behavior of aureomycin after its oral and intravenous administration to human beings. After the administration of therapeutically effective amounts of aureomycin, we were able to demonstrate antibacterial amounts of the material in the serum, cerebrospinal fluid, liver, kidneys and spleen, as well as pulmonary tissue. The blood serum of patients receiving multiple doses of aureomycin usually will reach a maximal concentration of approximately 4 μgm. per cc. It would appear that the rate of excretion of aureomycin is rather constant in the absence of any impairment of renal function, and there appears to be no "piling up" of the antibiotic in the serum of these patients.

Aureomycin readily traverses the blood-brain barrier and diffuses readily into the cerebrospinal fluid. It is, therefore, an effective agent in the treatment of infections of the central nervous system, including pyogenic infections, as well as neurosyphilis. Because of its acid pH and local irritation, it should never be introduced into the spinal canal. It diffuses readily through the placenta and is therefore available in the fetal circulation, a factor which is of importance in its possible value in the treatment of pyogenic infections, as well as prenatal syphilis. Fortunately, aureomycin diffuses readily into the pleura, and the pleural fluid content is approximately half that of the serum. It is, therefore, a useful agent in the treatment of infections of the pleura, but it should never be introduced into the pleural space. Furthermore, because of local irritation, aureomycin in its present form should not be used for nebulization.

Aureomycin is concentrated in the normal liver and is excreted in the bile. Large amounts of the antibiotic are constantly being excreted in the urine, but it should be emphasized that the amount of the material in the urine is no index of the amount of the substance present in the tissues. It is a useful antibiotic in the treatment of infections of the urinary tract, but for the reasons just mentioned it is by no means the final answer to the problem of the treatment of such infections, because, as I have already pointed out, the tissue content of aureomycin as well as that of any other antibiotic is undoubtedly of great importance in connection with the therapy of these infections. Some of the observations reported by Heilman and me[44] were confirmed by Dowling and his colleagues[30]. DeRoetth[82] reported some studies on the penetration of aureomycin into the eye. When compared with other antibiotics, aureomycin appeared to penetrate less readily into the eye, but once it had crossed the blood-aqueous barrier, it appeared to remain longer in the ocular fluids and tissues.

In connection with the absorption of aureomycin, the subject of aureomycin and aluminum hydroxide preparations has received some attention. According to diGangi and Rogers[36], aluminum hydroxide is capable of absorbing almost 100% of the antibiotic when assayed bacteriologically and colorimetrically. Waisbren and Hueckel[96] reported a very marked decrease of the content of aureomycin in the serum of patients who took aluminum hydroxide preparations with aureomycin. It is true that aluminum hydroxide preparations do interfere with the absorption of aureomycin, but therapeutically effective concentrations can be attained when 1 teaspoonful of aluminum hydroxide gel is used with each oral dose of 750 mg. of aureomycin. In any event, it is not necessary to use aluminum hydroxide preparations in

more than 10 to 20% of patients.

In addition to the method described by Heilman and me[44] for the estimation of aureomycin in various body fluids, a number of procedures have been described recently. It is impossible to assess the value of one method versus another. It would seem that the procedure to be adopted should be that which is most suitable for the particular laboratory in which the assays are being carried out. Methods have been described by Brainerd and associates[14], Schneierson and Toharsky[87], Levine and his colleagues[55], Randall and associates[73], Whitlock and his associates[98], and Saltzman[86].

In Vitro and In Vivo Activity. Demerec[29] reported some interesting studies which suggest that the pattern of aureomycin resistance is different from that of streptomycin resistance. He further pointed out that aureomycin resistance may be similar to penicillin resistance. These observations are in line with the clinical experience with aureomycin to date; namely, that the development of resistance has not been a major problem.

That aureomycin and penicillin are more active against gram-positive bacteria than is streptomycin or chloramphenicol was quite evident from the report of Pelcak and his co-workers[68]. Against gram-negative bacteria aureomycin was the most active of the antibiotics tested. In other words, of the 4 antibiotics mentioned, aureomycin appeared to be the most active against both classes of microbes. That aureomycin was not inhibited in the presence of blood or serum in the media was demonstrated by Beigelman[7]. A comparison of the bacteriostatic effect of aureomycin versus streptomycin against Brucella organisms was reported by Lacy and Lankford[52]. Under the conditions of their experiment no aureomycin-resistant mutants were selected from several strains of Brucella, in contrast to the fact that first stage mutants with high tolerance to streptomycin were yielded by the species examined. Fuller and Faust[35] reported that strains of Endamoeba histolytica grew in cultures containing the optimal amount of aureomycin as well as, if not better than, they grew in penicillin-streptomycin cultures. Steenken and Wolinsky[93] examined the *in vitro* and *in vivo* activity of aureomycin against Mycobacterium tuberculosis. It is quite obvious that under the conditions of their experiments the antibiotic had no deterrent effect upon the course of tuberculous disease in guinea pigs. These findings were confirmed by Perry[69]. Both studies just referred to suggest that the guinea pigs do not well tolerate aureomycin therapy.

That aureomycin possesses potent antirickettsial properties is apparent from the studies of Anigstein and his colleagues[1]. Results of these studies are in agreement with the previously reported observations of Wong and Cox[101]. Heilman[41] has reported a careful study of the action of aureomycin against Brucella infections in mice. It is evident from his studies that aureomycin exerts a very definite suppressive effect, but that Brucella organisms were not completely eliminated from the infected tissues after the use of this antibiotic alone. After comparing aureomycin alone and in combination with a number of other antibiotics, he concluded that the most suppressive effect on Brucella organisms is exerted by a combination of aureomycin and dihydrostreptomycin. That these original observations by Heilman were correct would seem indicated by results of similar studies subsequently reported by Magoffin and associates[62]. The latter studies were carried out on Brucella infections in the developing chick embryo.

Ransmeier[74] and also Larson[53] both reported studies which indicate that aureomycin is highly effective both *in vitro* and *in vivo* against Pasteurella tularensis. While results of these studies indicate that aureomycin should be investigated in the treatment of tularemia, it should be remembered that no therapeutic failures have occurred to date where streptomycin has been used against the disease. The advantage of aureomycin, however, would be that it can be effectively administered orally. Bradford and Day[13] found that aureomycin in rather large doses protects mice against experimental infections with Hemophilus pertussis. This action, however, was only bacteriostatic. Deaths frequently occurred in the animals after cessation of therapy. According to Wells and Finland[97], aureomycin appeared to be effective in the control of psittacosis in chick embryos. There appeared to be a direct relationship between the dose of the antibiotic and the prolongation of life. There is some evidence in this report to suggest that the prolongation of life after aureomycin therapy is a little more than the effect noted with chloramphenicol. That aureomycin has a slight suppressive effect against toxoplasmosis in mice was suggested by the report of Summers[95]. It was found in his experiment that para-aminobenzoic acid does not counteract the protective effect of aureomycin, which can be interpreted as simply indicating that the mode of action of the antibiotic is different from that of the sulfonamide compounds. Experimental melioidosis in guinea pigs is not influenced by treatment with aureomycin, according to Cruickshank[26]. It seems from the report of Baldridge and his colleagues[6], that aureomycin has no *in vitro* activity against herpes simplex virus. As compared with its activity against the larger viruses, a similar *in vivo* activity of aureomycin against herpes simplex could not be demonstrated.

Methods of Administration and Dosage. The recommended oral dose of aureomycin in the treatment of infections with organisms susceptible to its action is as follows. For adult persons, 750 mg. (3 capsules) should be administered every 6 hours. For children the recommended dose is 500 mg. (2 capsules) every 6 hours; for very young children and infants, 250 mg. (1 capsule) every 6 hours. A satisfactory method for administration of the material to infants is to mix the contents of the capsule with a teaspoonful of jam, jelly or some other foodstuff.

On occasion, reduction of the dose by half for a short period may lessen gastric irritation when it occurs. When aureomycin is to be administered for more than 7 to 10 days, it is recommended that vitamin supplements be given. A satisfactory method for the oral administration of aureomycin to patients who have intranasal catheters in place for suction is simply to include the contents of the capsule in a feeding formula and to administer the mixture. If the catheter is clamped for approximately 2 hours, absorption will occur.

If for any reason patients are unable to receive aureomycin orally, it may be desirable to administer it intravenously. Preparations of aureomycin for intravenous administration are now available. The recommended dose of aureomycin for intravenous use in adult persons is 500 mg., administered every 12 hours. This amount is dissolved in 250 to 300 cc. of saline solution. We have not found it necessary to use a buffer for the administration of aureomycin by this route. The material should be administered at a fairly rapid rate through an 18-gage intravenous needle. The foregoing amount

usually can be given in approximately 15 minutes. It should never be given by the intravenous drip method.

Aureomycin should not be injected into the veins of the lower extremities. The repeated injection of aureomycin produces venous irritation and thrombosis. This may in turn result in embolic phenomena. When aureomycin is used intravenously, it should always be injected into the veins of the upper extremities. Danger of embolic phenomena from the upper extremities is practically negligible. Intravenous aureomycin therapy should be used for not more than 2 or 3 days.

Considerable local irritation and pain result from the intramuscular injection of aureomycin, and in its present form the agent should not be given intramuscularly.

Clinical Studies on Aureomycin. Before discussing the general clinical indications for the use of aureomycin, I should like to mention aureomycin as an antibiotic of value in the prophylaxis of certain important infections. At the Mayo Clinic we have never subscribed to the widespread prophylactic use of antibiotics. In fact, the general procedure is to be condemned.

On the other hand, there are 2 or 3 important indications for the prophylactic use of antibiotics. One is the grossly and obviously contaminated peritoneum. Because of its wide range of activity, aureomycin is obviously of value in the prophylaxis and treatment of peritonitis.

The second condition in which the prophylactic use of antibiotics is justifiable is prevention of a recurrence of rheumatic fever. Since aureomycin is an exceedingly effective antibiotic agent when administered orally, it may well supplant penicillin for the prophylaxis of rheumatic fever. Its range of antibacterial activity is such that it should be recommended. A satisfactory amount is 250 mg. daily, given orally. Finally, it is my conviction that no patient with an organic heart lesion should undergo oral, intestinal, rectal or transurethral operative procedures without the benefit of at least 1 or 2 days of prophylactic therapy with penicillin or aureomycin.

It is difficult, from the examination of published material, to assess the value of aureomycin in the treatment of infections of virus origin. The report of Wright and associates[103] clearly indicates that aureomycin is of value in the treatment of lymphogranuloma venereum. This report was amply confirmed by Robinson and associates[80], and by Prigot and associates[71]. It should be remembered, however, that the organisms of the lymphogranuloma-psittacosis group are borderline, and that they may not remain in the classification of true viruses. On the other hand, rather convincing evidence concerning the clinical effectiveness of aureomycin in the treatment of herpes zoster is presented by Case[21], by Binder and Stubbs[12], and by Finland and his colleagues[33]. Concerning the possible value of aureomycin in infections caused by herpes simplex, it is difficult to make compatible the results of experimental studies discussed above and the clinical reports of Baer and Miller[4], Bereston and Carliner[9], and Arnold and associates[3].

There appears to be general agreement among a number of investigators[10,25,27,32,34,49,63,67,89] that aureomycin exerts a definite and beneficial effect on the course of different so-called viral or primary atypical pneumonias. One should bear in mind, however, that the virus of so-called atypical pneumonia has not been clearly isolated or identified. The published data contain little to support the

value of aureomycin in certain important viral infections, such as the common cold, influenza, poliomyelitis, encephalitis, variola and rubella. Evidence to date concerning its value against the plantar wart is by no means convincing.

In aureomycin it would appear that an effective agent is at hand for the treatment of the rickettsial diseases, including Q fever, typhus and Rocky Mountain spotted fever. That Q fever can be effectively treated thereby is evident from the report of Lennette and associates[54]. That aureomycin is more effective than para-aminobenzoic acid in the treatment of Rocky Mountain spotted fever is evident from the report of Ross and his associates[84]. Similar excellent results have been reported by Harrell and his associates[40], Gear and Harington[37], and Baker[5]. The report of Knight and his colleagues[50] leaves little doubt concerning the effectiveness of aureomycin in the treatment of typhus.

A number of reports have appeared concerning the value of aureomycin in the treatment of infections of the urinary tract and in the treatment of several important venereal diseases. Collins and Finland[24] were impressed with the value of aureomycin in the treatment of certain urinary infections. Carroll and his colleagues[20] concluded that aureomycin is effective in the treatment of infections of the urinary tract caused by E. coli, A. aerogenes, paracolon bacillus infections and infections caused by Streptococcus faecalis.

On the other hand, aureomycin obviously is no substitute for the elimination of foci and other abnormal conditions, including obstruction, which may be present in infections of the urinary tract. Most investigators are in agreement that aureomycin is of little value in the treatment of infections caused by Pseudomonas aeruginosa and species of Proteus. In favor of aureomycin over streptomycin is the fact that bacterial resistance does not readily occur. Rutenburg and Schweinburg[85] reported no evidence of the development of bacterial resistance in a series of infections of the urinary tract. The reports of Hill and associates[45], Robinson and his associates[78], Prigot and associates[71], and Greenblatt and his colleagues[38] contain information on the use of aureomycin in the treatment of 83 patients suffering from granuloma inguinale. Although in the past streptomycin has been reported to be of some value in the treatment of this infection, the results of the studies just mentioned leave little doubt that aureomycin is far more desirable than streptomycin in the treatment of granuloma inguinale. Chen and his colleagues[23] reported good therapeutic results from the use of aureomycin against gonorrhea. Yet no evidence is at hand to suggest the advisability of substituting aureomycin for penicillin in the treatment of infections with Neisseriae gonorrhoeae. In fact, the report of Robinson[77] would suggest that the rate of cure obtained with aureomycin may be less than that achieved with penicillin. That aureomycin is of value in the treatment of chancroid was suggested by Zheutlin and Robinson[106]. The experimental studies of Heilman mentioned previously clearly suggest that aureomycin possesses considerable antispirochetal activity. Other studies from the Mayo Clinic[48,65,66] clearly demonstrate that aureomycin is of considerable value in the treatment of early and late cutaneous syphilis and syphilis of the central nervous system.

Admittedly, penicillin is still effective in the treatment of syphilis. On the other hand, aureomycin supplies a new antibiotic for the treatment of this infection and, moreover, may be

employed for patients whose condition is resistant to penicillin or patients who are sensitive to penicillin. There is some evidence to suggest that aureomycin may be superior to penicillin in the treatment of syphilis of the central nervous system. Similar observations concerning the effectiveness of aureomycin in the treatment of syphilis have been reported by Irgang and Alexander[47], Wiggall and his co-workers[99], Rodriquez and associates[81], and Willcox[100].

The problem of resistance to penicillin on the part of microbes which originally were found to be susceptible to its action has been grossly exaggerated and overemphasized. There is one exception to this general statement. The number of strains of staphylococci which are resistant to penicillin which are being encountered has steadily increased during the past few years. Of the penicillin-resistant strains of staphylococci examined by Nichols and Needham, all were found to be sensitive to the action of aureomycin. Clinical reports by these investigators, as well as reports by Chandler and coworkers[22], clearly indicate that aureomycin is effective in the treatment of infections caused by penicillin-resistant strains of Micrococcus pyogenes.

That aureomycin has a definite suppressive effect on the course of culturally proved brucellosis is shown in the report of Spink and his associates[92], as well as in the reports of Bryer and associates[17], and Knight and his colleagues[50]. That aureomycin, on the other hand, is by no means a specific or uniformly curative agent can be seen easily in data subsequently published, including those of Spink and Yow[91]. There can be little doubt that the most effective method of treating culturally proved brucellosis to date is that described by Barber and me[43], in which aureomycin is combined with dihydrostreptomycin.

McVay and associates[60], and MacDonald[58] have reported on the successful use of aureomycin in the treatment of amebiasis. Their observations are interesting, but difficult to bring into line with the results of *in vivo* studies, mentioned earlier in this paper, in which aureomycin was used successfully to cultivate E. histolytica, unless it is postulated that cure of human amebiasis is contingent on the eradication of the bacteria from the intestinal flora, some of which are essential for the support of the amebas, which could no longer survive in the relatively sterile intestinal tract. A very comprehensive study on the effect of aureomycin on the bacterial flora of the intestinal tract of man has been reported by Dearing and Heilman[28]. It is clearly evident from their studies that aureomycin is the most effective agent available to date for the removal of bacteria from the intestinal tract. All bacteria culturable by the methods used by these investigators, except species of Proteus and Pseudomonas, were removed from the intestinal tract under the conditions of one of their experiments. Even Bacteroides species, present in large numbers in normal feces, were not found in the feces of 5 patients who received aureomycin. Specimens of feces from 5 untreated patients contained numerous Bacteroides organisms, under similar cultural circumstances. This is a real contribution to the preoperative preparation of patients. According to these investigators, the conditions which hindered or prevented removal of susceptible bacteria were perforated intestinal lesions, intestinal fistulas and intestinal obstruction.

Bell and his colleagues[8] suggested that aureomycin exerts a beneficial effect on the course of experimental pertussis and also human pertussis. On the other hand, Schoenbach[88] stated that aureomycin does not appear to be

effective against whooping cough. To date the matter is unsettled. The experimental studies referred to earlier, concerning the possible value of aureomycin in the treatment of tularemia, find confirmation in the clinical reports of Woodward and associates[102], Ransmeier and his co-workers[75], Carroll and Gorman[19], and Lindeke and Maiden[56], all of whom reported on the successful use of aureomycin in the treatment of human tularemia. Aureomycin, however, hardly can be expected to surpass the results already obtainable by the use of streptomycin against this infection. The lack of toxicity and ease of oral administration, however, probably favor the use of aureomycin.

Aureomycin has been investigated in the treatment of a number of infections of the skin. It has been used systemically and also in the form of an ointment. Various types of skin lesions have been reported to show favorable response. For example, Hollander and Hardy[46] were impressed by the value of aureomycin in the following types of conditions: infected ulcers, dermatitis, pyoderma, necrosis of the skin, pustular psoriasis and exfoliative lesions. According to Robinson and associates[79], a temporary suppressive effect was observed in dermatitis herpetiformis. Some evidence to support the notion that aureomycin is of value in the treatment of pemphigus appears in the reports by Philip[70], Natenshon[64], and Bettley[11]. Final assessment of the efficacy of aureomycin in the treatment of such a variety of infections must await more extensive studies.

That aureomycin may prove of value in the treatment of certain ocular infections, including dendritic keratitis, is suggested in the reports of Appelman and Hale[2], and Braley and Sanders[15].

The possible value of aureomycin in the treatment of a number of miscellaneous infections must be considered. That aureomycin may be of value in the treatment of infectious mononucleosis is suggested by Gruskin[39] and Lyons[57]. Unfortunately, a large, well-controlled study of the general subject has not yet appeared. The wide range of antibacterial activity of aureomycin, which includes its effectiveness against both gram-negative and gram-positive microbes, as well as species of Clostridia, commonly found in the intestinal tract, immediately suggests the value of this antibiotic in the prevention and treatment of acute suppurative peritonitis. The studies of Yeager and associates[105] on experimental peritonitis in dogs reveals the rather exciting comparison of a 90% survival rate in dogs treated with aureomycin, as compared with a 20% survival rate in the control animals. Their studies, as well as those of Wright and associates[104], in spite of the fact that the clinical experience is not large, are impressive enough to establish aureomycin as the antibiotic of choice in peritonitis. McVay and associates[59] have reported 2 instances in which septicemia due to Bacteroides organisms was treated successfully by the oral administration of aureomycin. In view of the experimental studies previously discussed, it is not surprising that Steinbach and his associates[94] found aureomycin to be of little or no value against pulmonary tuberculosis. The temporary clinical abatement of the pulmonary involvement of pancreatic fibrosis after aureomycin therapy which was noted by Shwachman and his colleagues[90] probably is best explained on the basis of the control of secondary infection, rather than by any effect upon the primary disease itself. Uniform disappearance of pleuropneumonia-like organisms from the genitourinary tract of patients was reported to follow the oral administration of aureomycin by Brown and associates[16]. This occurred in patients with and

without joint disease, and disappearance of the L organism followed the administration of aureomycin, whereas gold therapy had not eliminated the organism. No conclusions can be drawn concerning the possible value of aureomycin in the treatment of rheumatic diseases at this time. However, it might be pointed out that, using aureomycin in rats, Kuzell and associates[51] were able to cure experimental polyarthritis caused by the L4 strain of pleuropneumonia-like organism. On the other hand, it is not surprising that aureomycin produced no beneficial effects in several patients who had chronic rheumatoid arthritis.

Toxicity and Reactions. Like penicillin, aureomycin is remarkably free of serious toxic effects. In spite of widespread clinical experience of nearly 2 years' duration, only 2 reports have appeared at the time of this writing describing toxic cutaneous effects of aureomycin in 2 separate cases. One case was reported by Riese[76], the other by Rosanova and Warszewski[83].

Macht and Farkas[61] suggested that aureomycin may interefere with coagulation of the blood and thereby favor thrombo-embolic accidents. Although these observations are of interest, the hazard involved in the use of aureomycin on this basis is of little or no practical significance. Randall and his colleagues[72], reporting on the intravenous administration of aureomycin, found that, when the recommended intravenous dose of 0.5 gm. of aureomycin is exceeded, certain mild toxic effects may be experienced. On occasion, when as much as 1 gm. of aureomycin is administered intravenously at a single injection, nausea and vomiting may occur and mild febrile reactions may be induced.

It seems reasonable to conclude from the published data available at the time of this writing that aureomycin probably is the most versatile, as well as the most important, antibiotic agent that has been developed since the introduction of penicillin. Its low degree of toxicity, its ease of oral administration and the relative infrequent emergence of resistant strains of microorganisms susceptible to its action are features which place it in the category of an ideal antibiotic agent.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MARCH 21, 1950

Recordings of the Moving Spatial Forms in the Electrical Activity on Small Areas of the Cerebral Cortex of Cats and Monkeys. J. C. LILLY, M.D., and W. W. CHAMBERS, Ph.D. (Johnson Foundation and Dept. Anatomy, Univ. of Penna.). A new technique and some of the results of its use are described briefly. The Bavatron (A.I.E.E.-I.R.E. Symposium Volume on Instrumentation in Medicine and Nucleonics, to be published by the American Institute of Electrical Engineers in 1950) records some 2-dimensional cross sections of the 3-dimensional electrical activity of the brain (electro-iconograms). The input field is picked up by 25 electrodes in a 5 x 5 square array (8 mm. by 8 mm.) on the pia, is amplified by 25 amplifiers, and used to intensity-modulate 25 light sources in a 5 x 5 square array at the output. The moving and fixed figures and forms of the electrical input fields are thus transformed into corresponding patterns of variation of luminosity of the output field. The output field is photographed with a motion picture camera at 128 frames per sec. to obtain the records called electro-icono-grams or E.I.G.s.

By projecting the E.I.G.s at 16 frames per sec. on a screen subtending a visual angle of 0.1°, the following results can be seen by the observer: 1, in deep barbiturate anesthesia, the cortical responses to normal end organ stimuli can be seen to spread in the primary afferent areas in a stereotyped fashion from the zone first activated; 2, "barbiturate waves" are seen to be simple forms which travel or which "grow" around a focus and fade away in place; 3, spontaneous activity in the conscious animal has traveling, shifting figures of various velocities, sizes, and forms, depending grossly on previous stimuli.

Some Effects of Oxygen Inhalation at High Partial Pressures Upon Man. C. J. LAMBERTSEN, M.D., D. Y. COOPER, M.D., G. L. EMMEL, M.D., H. H. LOESCHCKE, M.D., R. H. KOUGH, M.D., and C. F. SCHMIDT, M.D. (Lab. of Pharmacol., Univ. of Penna.). In studies of the effects of inhalation of oxygen at high partial pressures (OHPP), samples of arterial and internal jugular blood were collected during air breathing at sea level and from the same subjects during oxygen inhalation at an ambient pressure of 3.5 atmospheres. Several subjects developed convulsive seizures due to toxicity of oxygen at the high arterial pO_2 produced. The table presents average results of measurements on 10 normal men. All changes produced by oxygen at 3.5 atmospheres were significant.

At 3.5 atmospheres the arterial plasma oxygen content of 6.5 vols. % almost met cerebral oxygen requirements, as indicated by the near-arterial level of internal jugular hemoglobin saturation. Hemoglobin base which becomes available for carbon dioxide transport by reduction of hemoglobin decreased 60%, producing an 8 mm. increase in A-V pCO_2 difference. The 3 mm. rise in venous pO_2 reflects an increased

Blood Measurements	Air, Sea Level		O_2, 3.5 A	
	Arterial	Venous	Arterial	Venous
O_2 Content (vols. %)	18.6	12.3	25.9	17.6
%Hb. Sat.	96.3	64.0	100.0	89.7
pO_2 (mm. Hg.)	—	37.	2360.	74.
CO_2 Content (vols. %)	50.0	56.0	46.9	55.2
pCO_2 (mm. Hg.)	40.	52.	35.	55.
pH	7.39	7.33	7.42	7.30

brain tissue pCO_2 which probably contributed to the decreased arterial pCO_2 by an increased pulmonary ventilation which was observed in subsequent experiments. Pulmonary irritation by oxygen has not been excluded as a factor in the respiratory stimulation. The small increase in venous pCO_2 indicates that retention of carbon dioxide in the brain during exposure to OHPP is not an important factor in acute oxygen poisoning.

Experience with Protein Bound Iodine (PBI); Effect of ACTH and Cortisone on Thyroid Function. JAMES D. HARDY, M.D., CECILIA RIEGEL, Ph.D., and ELEANOR P. ERISMAN, A.B. (Harrison Dept. of Surgical Research, Univ. of Penna.) There is general agreement that the PBI level of serum represents the concentration of the circulating thyroid principle. Using the permanganate method of Riggs and Man (Riggs, D. S., and Man, E. B.: J. Biol. Chem., **134**, 193, 1940) the PBI levels of serum were determined on normal subjects, patients with thyroid disease and patients receiving ACTH and cortisone therapy. The PBI levels in normal subjects ranged from 3 to 6γ%. These findings agree well with those reported by other workers using the same method. Patients having abnormal thyroid activity presented values ranging from as low as 1γ% in a cretin to 16γ% in a markedly thyrotoxic subject. In general, the thyrotoxic patients presented values above 8γ% and below 13γ%. One patient in whom a total thyroidectomy was done had a preoperative level of 6γ% and a level of 1γ% 5 weeks after operation. This observation is in accord with the finding of low concentrations of PBI in the serum and tissues of thyroidectomized animals (Chaikoff, I. L., Taurog, A., and Reinhardt, W. O.: Endocrinology, **40**, 47, 1947; Morton, M. E., Chaikoff, I. L., Reinhardt, W. O., and Anderson, E.: J. Biol. Chem., **147**, 757, 1943).

The administration of ACTH or cortisone to patients with lupus erythematosus or rheumatoid arthritis was followed by a diminution in the serum level of PBI in 5 cases in whom both pre- and post-treatment serum levels were obtained. In 4 cases in whom no pretreatment level was obtained the concentrations were abnormally low immediately following therapy. In only 1 case (liver disease) did the PBI level rise and in this case the second specimen was obtained not until 5 weeks after the first. The course of treatment usually lasted 7 to 10 days.

The exact mechanism by which ACTH and cortisone act to decrease the serum level of PBI is not certain. On the basis of work reported by others (Paschkis, K. E., Cantarow, A., Eberhard, T., and Boyle, D.: Proc. Soc. Exp. Biol. and Med., **73**, 1, 116, 1950; Riggs, D. S., and Man, E. B.: J. Biol. Chem., **134**, 193, 1940; Soffer, L. J., Gabrilore, J. L., and Jailer, J. W.: Proc. Soc. Exp. Biol. and Med., **71**, 117, 1948) it would seem possible that the adrenal cortex exerts an inhibitory effect on the thyrotropin stimulating effect of epinephrine. But whatever

the factors involved, it is important to realize that the effects of ACTH and cortisone are widespread and that the beneficial effects resulting from the administration of these compounds may be mediated through multiple metabolic processes.

The Stimulating Effect of Xanthines on the Aerobic Formation of High Energy Phosphate. B. D. Polis, Ph.D., E. Polis, and L. Jedeikin (Diabetic Coma Project, Phila. Gen. Hosp.). One of the key pathways for biological energy formation and utilization is the accumulation of high energy phosphate bonds in adenosine-triphosphate as a result of the oxidation of Krebs' cycle metabolites. To evaluate various factors regulating the velocity of these reactions, a preparation of mitochondria from rat liver was used, that esterified inorganic phosphate to high energy phosphate levels while oxidizing γ-keto-glutaric acid. This reaction was opposed with a MgATPase preparation degrading high energy phosphate. As an indicator system yeast hexokinase was added to transfer the high energy phosphate from ATP, as formed, to glucose. In this manner a measure of high energy phosphate formed over a given time interval is obtained by determining the decrease in inorganic phosphate. The ratio of phosphate esterified over the oxygen consumed becomes a measure of the efficiency of the oxidative process in providing useful biological energy.

In a series of 26 rat liver preparations, the addition of 1.4×10^{-4} Molar Xanthine to the enzyme substrate mixture produced a statistically significant increase in the amount of phosphate esterified, averaging a 101% increase over that of the control. The efficiency of the phosphorylating mechanism (P/O_2) was increased by an average value of 63% over the controls.

Studies of the oxygen uptake and phosphate esterified were made varying time, pH and concentration of the purine. Optimal conditions for demonstration of the stimulating effect were found at pH 7.2 with 30 min. incubation period. The pH activity curve with Xanthine was shown to vary markedly, both quantitatively and qualitatively, compared with the control.

Rating the increase in phosphorylation with Xanthine as 100, the relative stimulating effects of other purines were as follows: Adenine 90, hypoxanthine 57, Uric acid 30, Caffeine 153 and Aminophylline 126 at equimolar concentrations of the purines.

The hypothesis was proposed that purines, like creatine, may serve as a high energy phosphate reservoir, thus implying that purines constitute another type of high energy phosphate compound.

A Method of Studying the Attenuation of Alternating Sinusoidal Currents Introduced into the Heart in Life and Death. J. H. Hafkenschiel, M.D., A. J. Neumann, M.S., C. F. Kay, M.D., E. L. Foltz, M.D., D. D. Talley, M.D., and H. F. Zinsser, M.D. (Robinette Foundation, Sch. of Med., and the Moore Sch. of Electrical Engineering, Univ. of Penna.) Field theory applied to electrocardiography aims to delineate the spatial orientation of electrical forces of cardiac origin. Calculated orientations are based upon the assumption that the heart acts as a dipole immersed in an approximately homogeneous electrical medium, that the arms and left leg are approximately equidistant electrically from each other and from the dipole, and that additional body surface points may be employed for orthagonal orientation. Quantitative determination of the degree by which calculated orientations

diverge from true orientations requires investigation of the magnitude of error inherent in each of these assumptions. Although ultimately feasible with a living human, the cadaver should provide a practical substitute if the relationship between conductivity and distribution in the living can be quantitatively correlated with that in the dead.

Sinusoidal 20 cps currents were impressed upon the hearts of anesthetized dogs through dipoles placed by catheterization of the right ventricle and coronary sinus. These dipoles were shown to lie approximately at right angles to each other in serial anteroposterior and lateral chest Roentgen-rays. Potential differences between various positions on the body were measured electrocardiographically.

Measurements were made as input current was increased until ventricular fibrillation occurred. Further measurements were made up to 24 hours after death. Measurable surface potential differences were obtained with input voltages of .2 volt and input current of 0.2 milliampere. An input of approximately 1 volt with a current of 1 milliampere was sufficient to induce ventricular fibrillation and death. Potential differences between peripheral points increased linearly with input current in any series of measurements. A gross correlation existed between dipole orientation and magnitude of measurements from peripheral leads. The relation of input voltage to output voltage (attenuation) does not change after death by more than 175%. It seems probable that this change is largely a result of factors other than alterations in tissue conductivity. This method will be used in conductivity studies in cadavers, in the attempt to define the magnitude of error in field theory assumptions, if further animal experiments with a better output measuring device support these tentative conclusions.

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BOOK REVIEWS AND NOTICES

CLINICAL AUDIOLOGY. By MAURICE SALTZMAN, M.D., Ass't Prof. of Otorhinology, Temple Univ. Pp. 195; 82 figs. New York: Grune & Stratton, 1949. Price, $5.00.

THIS book has 5 chapters under the following headings: Sound and Noise, Hearing, Deafness, Hearing Tests and Hearing Aids. Under each chapter sub-topics are briefly described. It is hardly possible in so short a book containing 82 graphs to discuss any of the topics to the point of completeness or even clarity. The book is too brief and contains few thoughts not already present and well explained in the numerous textbooks on Otolaryngology. The chapter on Hearing Aids, however, is very much worth while.

Comparatively few references since 1945 are used by the author despite the fact that major contributions and changes have occurred since then. Many statements have no specific reference to them and are in disagreement with generally accepted thoughts. For example, on the first page the Author states about the ear "In frequency range the lower limit is 12 d.v. per sec. and the upper limit is 41,000 d.v. per sec." Men such as Fletcher, L. A. Watson, and H. Davis, who have done actual determinations, state that although adults can hear only up to 16,000 cycles, some children may hear up to 25,000 cycles. Even this, of course, is very different from the 41,000 quoted by the Author. Scattered throughout the book are such questionable statements without cited references. In the Reviewer's opinion this book has but limited use in the field. J. S.

CHEMICAL ACTIVITIES OF THE FUNGI. By JACKSON W. FOSTER, Univ. of Texas. Pp. 648; 34 ills. New York: Academic Press, 1949. Price, $9.50.

THE Author of this authoritative addition to the biochemical literature on micro-organisms is well qualified, through both academic and industrial experience, to discuss the theoretical and the practical aspects of mold metabolism. In addition to a valuable chapter devoted to the techniques of culturing and preparing fungi for study, there are numerous references throughout the text to practical techniques, as, for instance, the isolation of mutants. A general discussion of various pathways of carbohydrate metabolism is succeeded by single chapters on some compounds most frequently encountered as by-products, namely lactic acid, oxalic acid, citric acid, and others. There is a section on natural variation and spontaneous and induced mutations. The trace-element nutrition of fungi is discussed. The utilization and metabolism of nitrogen and other elements is followed by a section on the various aspects of the production of penicillin, the only antibiotic presented.

The layman in this field will find much of theoretical interest and workers actively concerned in the microbiology of fungi will find much of practical interest. A. D.

A TEXTBOOK OF SURGERY. Edited by FREDERICK CHRISTOPHER, M.D., Prof. of Surgery, Northwestern Univ. Med. School. 5th ed. Pp. 1550; 1465 ills. Phila.: W. B. Saunders, 1949. Price, $13.00.

THIS is the 5th edition of one of the best text books ever published on surgery. Dr. Christopher has edited a volume that has been written by a large number of the surgical teachers in America. Each section has a brief bibliography so that the student can readily go further into a subject. I cannot recommend it too highly for use in the teaching of surgery. I. R.

RESUSCITATION AND ANESTHESIA FOR WOUNDED MEN. By HENRY K. BEECHER, M.D., Prof. of Research in Anesthesia, Harvard. Pp. 179, 58 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $5.50.

THIS monograph is based on a large experience gained at first hand while aiding in the treatment of the wounded soldier. The pathological physiology of the immediate physical insult to the body is discussed, and methods of treatment are aptly presented. A brief, concise and valuable discussion of the problems these individuals present in anesthesia is included. There are many good charts and tables and the conclusions drawn by the Author are all well documented.

The book can be unreservedly recommended to the physician who might at any time be called upon to manage traumatic shock in civilian practice. P. D.

ROENTGEN DIAGNOSIS OF DISEASE OF THE SKULL. By MAX RITVO, M.D., Ass't Prof. of Radiology, Harvard Medical School. Annals of Roentgenology Vol. XIX. Pp. 409; 466 ills. New York: Paul B. Hoeber, 1949. Price, $16.00.

THIS book is largely an atlas showing some of the lesions that can be demonstrated by the Roentgen examination of the head. The publisher has provided large illustrations, which are helpful, but in many of them either the original was poor or the quality of the paper prevents good definition of what the Author is trying to demonstrate. This is most unfortunate because one of the chief values of this type of publication is its illustrations. Other portions of the book are weak, from this Reviewer's standpoint, in having too few illustrations. A glaring example of this deficiency is in the chapter on Intracranial Calcifications. There are a number of excellent articles on this subject; for instance, those by Dr. John Camp. The reader, who will usually be the radiologist, would welcome more in this particular field should a 2d edition be published.

The general make-up of the book is good, the printing is excellent, but the illustrations are, in fact, poor. E. P.

CLINICAL BIOCHEMISTRY. By ABRAHAM CANTAROW, M.D., Prof. of Biochemistry, Jefferson Medical College, and MAX TRUMPER, Ph.D., Commander, H(S), USNR, Nat'l Naval Medical Center, Bethesda, Md. 4th ed. Pp. 642; 38 ills. Phila.: W. B. Saunders, 1949. Price, $8.00.

THIS edition impresses the Reviewer as being greatly superior to the preceding, since extensive and often overdue revisions of nearly all topics have been made. Some 1947 references are included. It will serve effectively both the student who wishes to gain the essentials without excessive detail and the clinician who seeks specific answers to actual clinical problems. J. R.

AN ATLAS OF AMPUTATIONS. By DONALD B. SLOCUM, M.D., M.S., Sacred Heart Genl. Hosp., Eugene, Oregon. Pp. 562; 564 ills. St. Louis: C. V. Mosby, 1949. Price, $20.00.

DURING World War II Surgeon General Kirk established amputation centers in several army general hospitals for the segregation, study, and treatment of army amputees. The immense experience gained by surgeons in these centers—unequaled during times of peace—forms the basis of this book by Dr. Slocum, who is former Chief of the Amputation Section at the Walter Reed General Hospital.

His atlas is concerned primarily with amputations performed because of trauma rather than for malignant or degenerative diseases. Operative technique is exhaustively covered. The sections on rehabilitation and prosthesis are complete and contain much material not presented by previous books on amputation. The illustrations, chiefly photographs of amputees at the Walter Reed Hospital, are abundant. All surgeons who perform amputations should have the book available for reference. W. F.

QUANTITATIVE ULTRAMICROANALYSIS. By PAUL L. KIRK, Ph.D., Prof. of Biochemistry, Univ. of California. Pp. 310; 113 figs. New York: John Wiley & Sons, 1950. Price, $5.00.

IN biological research the small-scale analysis of isolated systems or individual cellular components is the goal to which much current effort is directed. Ultramicrochemistry is that specialized discipline in such procedures of analytical chemistry. The Author is one of the most active investigators and teachers of these specialized techniques. This volume presents detailed directions for analysis of many individual substances by titrimetric, spectrophotometric and volumetric gas methods. It is recommended to all who are concerned with the problems of chemical analysis. H. V.

OFFICE ORTHOPEDICS. By LEWIS COZEN, M.D., Ass't Prof. of Orthopedic Surgery, College of Medical Evangelists, Los Angeles. Pp. 232, 156 ills. Phila.: Lea & Febiger, 1950. Price, $5.00.

THIS must have been a difficult book to write because it attempts to cover the conservative care of the large number of subjects embraced under orthopedic surgery. According to the Author, the book is intended to give in sufficient detail information on simple therapeutic methods. The Reviewer thinks that a book of this scope could well include more instruction on the examination of the normal in comparison with the abnormal joint. It should find a place in giving the rudiments of the specialty to interns, residents and nurses as well as an aid to the general practitioner. P. C.

NEW BOOKS

Audiology. By NORTON CANFIELD, M.D., Assoc. Prof. of Otolaryngology, Yale Univ. School of Medicine. Pp. 45. Springfield, Ill.: Charles C Thomas, 1949. Price, $1.75.

Electronics: Experimental Techniques. By WILLIAM C. ELMORE, Assoc. Prof. of Physics, Swarthmore College, and MATTHEW SANDS, Ass't Prof. of Physics, Massachusetts Institute of Technology. Pp. 417. New York: McGraw-Hill, 1949. Price, $3.75.

Lehrbuch der Klinischen Hämatalogie. VON PROF. DR. HANS SCHULTEN. Pp. 470; 78 ills. 42 in color. Stuttgart: Georg Thieme Verlag; imported by Grune & Stratton, 1949. Price, $11.00.

Differentialdiagnose der Inneren Medizin. By NAEGELI. Pp. 794; 190 ills. Stuttgart: Georg Thieme Verlag; imported by Grune & Stratton, 1949. Price, $9.00.

The Chemistry of Penicillin. Report on a Collaborative Investigation by American and British Chemists. Edited by HANS T. CLARKE, JOHN R. JOHNSON, and SIR ROBERT ROBINSON. Pp. 1094. Illustrated. Princeton, N. J.: Princeton Univ. Press, 1949. Price, $36.00.

Coronary Artery Disease. By ERNST P. BOAS, M.D., Assoc. Physician, Mt. Sinai Hospital, New York, and NORMAN F. BOAS, M.D. Pp. 399; 88 ills. Chicago: Year Book Publishers, 1949. Price, $6.00.

Aviation Medicine in its Preventive Aspects. An Historical Survey. By JOHN F. FULTON, M.D. University of London Heath Clark Lectures 1947. Pp. 174; 43 ills. New York: Oxford University Press, 1949. Price, $3.50.

Hormones in Clinical Practice. By H. E. NIEBURGS, M.D., Ass't Prof., Univ. of Georgia. Pp. 388; 57 ills. New York: P. B. Hoeber, 1950. Price, $5.50.

THE 16 chapters of this outline of the physiology and clinical uses of the hormonal endocrine secretions deal with the pituitary, thyroid, parathyroid, adrenals, pancreas, gonads, vitamin-endocrine relationships, diagnostic procedures and the therapeutic use of non-hormonal substances in endocrine disorders. There is also a list of commercial hormone preparations, many of which are of British manufacture and some of which are not available at present. The style is clear and simple, but there is some tendency to over simplification, especially in the treatment of certain moot physiological relationships. E. R.

Manual of Medical Emergencies. By STUART C. CULLEN, M.D., Prof. of Surgery, and E. G. CROSS, M.D., Prof. of Pharmacology, State Univ. of Iowa College of Medicine. Pp. 267; 29 ills. Chicago: Year Book Publishers, 1949. Price, $3.75.

Advances in Carbohydrate Chemistry. Vol. 4. Edited by W. W. PIGMAN, Univ. of Alabama and M. L. WOLFROM, Ohio State Univ. Pp. 378. New York: Academic Press, 1949. Price, $7.80.

TEN SUBJECTS include the structure and configuration of several carbohydrates, wood saccharification, boric acid in the determination of carbohydrate configuration, the hexitols, plant gums and mucilages, and the utilization of sucrose. Reviews of blood group polysaccharides, and biochemical reductions at the expense of sugars, are of special interest to biologists. H. V.

Bowery to Bellevue. By EMILY DUNNING BARRINGER, M.D. Pp. 262. New York: W. W. Norton, 1950. Price, $3.00.

THE story of New York's first woman ambulance surgeon.

Grundriss der Allergie. Von Dr. med. RUDOLPH ABDERHALDEN. Pp. 179. Basel: Benno Schwabe, 1950. Price, Geb. fr. 14.50.

The Common Infectious Diseases. By H. STANLEY BANKS, Physician-Supt., Park Hospital, Hither Green, London. Pp. 354; 90 ills. Balt.: Williams & Wilkins, 1949. Price, $4.50.

Advances in Protein Chemistry. Edited by M. L. ANSON, JOHN T. EDSALL, and (for the British Isles) KENNETH BAILEY. Vol. 5. Pp. 481. New York: Academic Press, 1949. Price, $7.50.

THIS fifth annual volume of selected topics in protein chemistry contains many reviews of biochemical and general interest as indicated by the following titles: The Synthesis of Peptides; Amino Acid Composition of Purified Proteins; Biological Evaluation of Proteins; Milk Proteins; Plant Proteins; Synthetic Fibers Made from Proteins; Some Protein-Chemical Aspects of Tanning Processes; and Protein, Lipids, and Nucleic Acids in Cell Structures and Functions. H. V.

Heavy Metal Prosthetic Groups and Enzyme Action. By OTTO WARBURG. Translated by ALEXANDER LAWSON. Pp. 230; 49 figs. London and New York: Oxford University Press, 1950. Price, $3.75.

THIS book is primarily of interest as a historical review of researches by Warburg and others on the role of iron in cellular oxidations. The last 2 chapters are concerned with the Author's investigations of the photochemical reduction of quinone by green cells and with his previously unpublished work on the quantum requirement of carbon dioxide assimilation. M. C.

NEW EDITIONS

Essentials of Obstetrical and Gynecological Pathology. By ROBERT L. FAULKNER, M.D., Ass't Prof. of Gynecology, and MARION DOUGLASS, M.D., Formerly Ass't Prof. of Gynecology, Western Reserve Medical School. 2d ed. Pp. 357; 300 ills., 3 in color. St. Louis: C. V. Mosby, 1949. Price, $8.75.

Questions, Medical State Board, and Answers. By R. MAX GOEPP, M.D., Formerly Prof. of Clinical Medicine, and HARRISON F. FLIPPIN, M.D., Assoc. Prof. of Med., Graduate School, Univ. of Penna. 8th ed. Pp. 663. Phila.: W. B. Saunders, 1950. Price, $7.00.

Urologic Roentgenology. By MILEY B. WESSON, M.D., Past Pres. Am. Urol. Assn. 3d ed. Pp. 282; 366 ills. Phila.: Lea & Febiger, 1950. Price, $7.50.

IN rewriting his book Dr. Wesson has prepared a compact volume which should be of real value to the urologist and the radiologist. The Author has included a number of cases from his own and his friend's files. The illustrations are beautifully done and aid one greatly in interpretation of puzzling cases.

The previous editions were excellent; this one maintains the same high standard. The publishers have done a fine job. In this small volume, the Author has covered every field in a most satisfactory manner. E. P.

Green's Manual of Pathology. Revised by H. W. C. VINES, M.D., Prof. of Pathology, Univ. of London. 17th ed. Pp. 1200; 730 ills. Balt.: Williams & Wilkins, 1949. Price, $8.00.

THIS edition of an English publication has been extensively altered. The material is presented in a precise, didactic fashion, which makes for quick ready reference. The Author puts less insistence upon detailed descriptions. H. V.

Practical Neurological Diagnosis. By R. GLEN SPURLING, M.D., Clin. Prof. Surg. (Neurosurg.), Univ. of Louisville. 4th ed. Pp. 267; 101 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $5.00.

DOCTOR Spurling has adhered to his plan to keep this work a simple, practical guide to neurological diagnosis. A glossary of common neurological terms is included. It is not difficult to understand why there has been such a demand for his work, for it is so concise and clear that it must be of great aid to the internist and general practitioner. The publishers are to be congratulated upon the superior printing of the volume. I. R.

A Text-book of Neuro-anatomy. By ALBERT KUNTZ, Ph.D., M.D., Prof. of Anatomy, St. Louis Univ. 5th ed. Pp. 524; 331 ills. Phila.: Lea & Febiger, 1950. Price, $8.00.

No better recommendation can be given any textbook of Neuro-Anatomy than that it required a 5th edition. The Author has attempted to bring the book up to date. This is always a difficult task and requires many a compromise which can rarely be solved to everybody's satisfaction. F. L.

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CORRECTION

Table 1 of the article on Lipotropic Effect of Liver Extract (*219*, 198, 1950) should read: Diet II: Salt Mixture 3%; Lard 6%; Sucrose 15%. Diet III: Salt Mixture 3%; Casein 4%; Lard 6%; Sucrose 15%.